PDF version

Ali Khamesipour,[1] Akram Mohammadi,[1] Mahmoud Jaafari,[2,3] Seyed Eskandari,[1] Minoo Tasbihi,[1]
Amir Javadi,[1,4]
Farzaneh Afshari,[5]
Hossein Mortazavi[6]
and Alireza Firooz[1]

[1]Center for Research and Training in Skin Diseases and Leprosy, Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran (Correspondence to: A. Khamesipour: Ali.Khamesipour@gmail.com). [2]Department of Pharmaceutical Nanotechnology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Islamic Republic of Iran. 3Nanotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Islamic Republic of Iran. [4]Department of Social Medicines, Qazvin University of Medical Sciences, Qazvin, Islamic Republic of Iran.
[5]ExirNanoSina Co., Tehran, Islamic Republic of Iran.
[6]Department of Dermatology, Tehran University of Medical Sciences, Razi Hospital, Tehran, Islamic Republic of Iran.

Abstract

Background: Topical nanoliposomes containing 0.4% amphotericin B (Lip-AmB 0.4%) have shown promising safety results in preclinical and phase 1 clinical trials in healthy volunteers.

Aims: To evaluate safety and efficacy of Lip-AmB 0.4% in cutaneous leishmaniasis patients.

Methods: Fourteen patients with a total of 84 lesions received national standard treatment of

weekly intralesional meglumine antimoniate with biweekly cryotherapy, or daily intramuscular meglumine antimoniate (20 mg/kg/day for 14 days), and topical Lip-AmB 0.4% twice daily for 28 days. Twenty-two patients with a total of 46 lesions (7 at most) were treated with topical Lip-AmB 0.4% alone twice daily for 28 days. Thirty patients with a total of 68 lesions received national standard treatment of weekly intralesional meglumine antimoniate (to blanch around the lesion) and biweekly cryotherapy.

Results: Sixty-six patients with cutaneous leishmaniasis lesions completed the study. In the safety evaluation, 2 of the 36 patients evaluated reported a tolerable burning sensation and they preferred to continue treatment. Twelve (92%) of 14 patients with 84 lesions who received national standard treatment combined with Lip-AmB 0.4% completed the study with complete cure. In 1 of the patients with 4 lesions, 1 lesion showed complete cure and 3 showed partial cure. Among 22 patients with 46 lesions who received only topical LipAmB 0.4%, 19 completed the study and 18 showed complete cure (95% efficacy). In the 30 patients who received national standard treatment alone, 33 lesions in 15 patients showed complete cure (48.5%) on day 42 follow-up.

Conclusion: Lip-AmB 0.4% alone or in combination with national standard treatment is safe with high-efficacy rate and warrants further investigation during phase 3 clinical trials.

Keywords: nano, liposomal, amphotericin B, cutaneous, leishmaniasis, Glucantime, Iran

Citation: Khamesipour A; Mohammadi A; Jaafari M; Eskandari S; Tasbihi M; Javadi A; et al. Pilot study of safety and efficacy of topical liposomal amphotericin B for cutaneous leishmaniasis caused by Leishmania major in Islamic Republic of Iran. East Mediterr Health J. 2022;28(9):658–663. https://doi.org/10.26719/emhj.22.070

Received: 30/11/21; accepted: 11/05/22

Copyright © World Health Organization (WHO) 2022. Open Access. Some rights reserved. This work is available under the CC BY-NC-SA 3.0 IGO license (https://creativecommons.org/licenses/by-nc-sa/3.0/igo)

Introduction

Cutaneous leishmaniasis is the most common form of leishmaniasis and it is endemic in about 90 countries, with 600 000 to 1 million new cases annually. According to the World Health Organization (WHO), more than 90% of cutaneous leishmaniasis cases reported in 2019 were from Afghanistan, Algeria, Brazil, Colombia, Islamic Republic of Iran, Iraq, Libya, Morocco, Pakistan, Peru, Syrian Arab Republic and Tunisia (1). Cutaneous leishmaniasis is a vector-borne parasitic disease caused by different Leishmania species and transmitted through sand fly bites, specifically in uncovered parts of the body. The most common species of the parasite include Leishmania major, Leishmania tropica, Leishmania infantum and Leishmania donovani, which are found in many geographical areas such as North Africa, Mediterranean, Middle East, Indian Subcontinent and Central Asia (1,2).

Cutaneous leishmaniasis causes skin lesions with various clinical features from slow-healing lesions to permanent scars (3), resulting in social stigma and psychological disorders that negatively affect the quality of life (4). Standard treatment for cutaneous leishmaniasis currently depends on multiple injections of antimoniate derivatives. However, several alternative therapies are under investigation because of the challenges of antimoniate derivatives, including injection site pain, high cost, severe adverse effects, variable efficacy and drug resistance. Oral treatments such as azole antifungal drugs, dapsone, azithromycin, miltefosine and zinc sulfate have been evaluated for treatment of cutaneous leishmaniasis but are associated with adverse effects and variable efficacy (2–7). Topical formulations have been developed against cutaneous leishmaniasis and tested in clinical trials but they are not yet available in the market (8–10). Amphotericin B (AmB) is a polyene antifungal agent that kills pathogens by binding to ergosterol and causing subsequent pore formation in the cell membrane and oxidative damage. Despite the effectiveness of AmB against fungal infections and visceral leishmaniasis, its use is limited because of the significant toxicity, especially nephrotoxicity and infusion-related reactions (11). To reduce the adverse effects and increase tolerance to AmB, 3 lipid-based formulations have been developed (Amphotec, Abelcet and AmBisome) to treat visceral leishmaniasis but their efficacy for cutaneous leishmaniasis is not high (11–13). Therefore, novel formulations with optimal skin penetration are needed to improve cutaneous leishmaniasis treatment.

Liposomes are spherical biodegradable vesicles that are extensively used because of their safety and improved delivery. Numerous studies have revealed that topical liposomal formulations reduce adverse effects and improve skin penetration and on-site drug accumulation (13,14). Nanoliposomes containing 0.4% amphotericin B (Lip-AmB 0.4%) have been developed under good manufacturing practice guidelines using phosphatidylcholine and cholesterol for treatment of cutaneous leishmaniasis. The formulation demonstrated promising results against L. tropica and L. major in vitro and L. major in vivo (15) and shown to be safe in animal models (16). The safety of Lip-AmB 0.4% has been evaluated in healthy volunteers in a

phase I clinical trial. The skin before and after topical application of Lip-AmB 0.4% twice daily showed no significant difference in hydration, transepidermal water loss, melanin, erythema, temperature, sebum and pH (17). Another clinical study showed no significant difference in the safety and efficacy of Lip-AmB 0.4% compared to intralesional injection of meglumine antimoniate in cutaneous leishmaniasis patients (18). In the current study, we compared the safety and efficacy of topical Lip-AmB 0.4% alone, topical Lip-AmB 0.4% combined with meglumine antimonate, and meglumine antimonate plus cryotherapy for treatment of cutaneous leishmaniasis lesions.

Methods

Study design

This was an open, pilot clinical trial, registered at the Center for Research and Training in Skin Diseases and Leprosy (CRTSDL), conducted in accordance with guidelines for good clinical practice. Ethical approval was obtained from the institutional ethics committees at CRTSDL, and informed consent was obtained from all candidates before enrolment. The study objectives and procedures were explained to the patients and the treatment option was selected based on the patient's wishes and physician's decision. The study evaluated the safety and efficacy of the following treatments for cutaneous leishmaniasis lesions caused by L. major: topical Lip-AmB 0.4% alone, topical Lip-AmB 0.4% combined with meglumine antimonate, and meglumine antimonate plus cryotherapy.

Study patients

The inclusion criteria were: (1) age 14–60 years; (2) parasitologically confirmed cutaneous leishmaniasis lesions caused by L. major using direct smear, culture and polymerase chain reaction (PCR); and (3) clinical diagnosis of up to 5 cutaneous leishmaniasis lesions with a diameter

Exclusion criteria were: (1) pregnancy or patients not willing or unable to use contraceptives during and 3 months after the end of therapy; (2) lactation; and (3) using any other treatment for cutaneous leishmaniasis. Initially 46 patients were enrolled to receive Lip-AmB 0.4% based on the inclusion/exclusion criteria. Ten patients were excluded for the following reasons: (1) 2 patients' lesions were not confirmed parasitologically using direct smear, culture and PCR; (2) lesions in 6 patients were caused by L. tropica; and (3) 2 patients developed sporotrichoid lesions. Thirty-six patients completed the study.

Drug administration

Lip-AmB 0.4% was produced under good manufacturing practice conditions at Razaak Arak Pharmaceutical Company (Tehran, Islamic Republic of Iran). The production was supported by DNDi (Geneva, Switzerland). Glucantime (meglumine antimonate) was produced by Sanofi Aventis (France). Fourteen patients with a total of 84 lesions received national standard

treatment of weekly intralesional meglumine antimonate (7 IL injections) plus biweekly cryotherapy (3 or 4 sessions), or daily intramuscular meglumine antimonate (20 mg/kg) per day for 14 days plus topical Lip-AmB 0.4% twice daily for 28 days. Twenty-two patients with a total of 46 lesions (7 each at most) were treated with topical Lip-AmB 0.4% alone twice daily for 28 days. Thirty patients aged 14–60 years with a total of 68 lesions received national standard treatment of weekly intralesional meglumine antimonate (7 IL injections) plus biweekly cryotherapy (3 or 4 sessions).

Study procedures

At baseline before treatment initiation and at each of the weekly visits up to day 28 of follow-up, patients were given a written instruction to rub each of their lesions with Lip-AmB 0.4%, twice daily in the morning and at night. During each weekly visit, the Lip-AmB 0.4% tubes were replaced with new ones and the old ones were collected and kept till the end of the study.

Measurement of lesions

At baseline, each patient was interviewed for demographic and health backgrounds. The number, location and type of each lesion were recorded and the lesions were measured in 2 dimensions using a digital calliper. The details were entered into a computer and after double entry, the data were cleaned and analysed by the data management team. The lesion specifications were recorded during each visit and a standardized digital photograph was taken.

Results

Treatment safety

Safety evaluation in 36 patients, aged 19–60 years (20 female and 16 male) showed no adverse events such as itching, burning, inflammation, or pain at the lesion site. In 2 other patients with lesions > 15 cm, topical treatment with Lip-AmB 0.4% induced a burning sensation that was tolerable and the patients preferred to continue treatment.

Treatment efficacy

Fourteen patients, aged 24–51 years (8 female and 6 male) with 84 lesions received national standard treatment (weekly intralesional meglumine antimonate and biweekly cryotherapy, or daily intramuscular meglumine antimonate plus topical Lip-AmB 0.4% twice daily for 4 weeks). Follow-up was conducted on 12 of the patients, and on day 42 after treatment initiation, 11 showed complete cure (91.7% efficacy). In 1 of the patients with 4 lesions, 1 lesion showed complete cure and 3 showed partial cure at 42 days after initiation of treatment. Twenty-two patients, aged 28–51 years (13 female and 9 male) with 46 lesions (7 lesions each at most) were treated with topical Lip-AmB 0.4% alone twice daily for 4 weeks. One patient did not take the treatment and 2 were not available for follow-up visits. Thus, 19 patients completed the

study according to the protocol. On day 42 after treatment initiation, 18 patients with 36 lesions showed complete cure (94.7% efficacy). Among the 30 patients who received standard treatment alone, 15 (50% efficacy) showed complete cure on day 42 after treatment initiation. On day 42, in the patients who received standard treatment plus Lip-AmB 0.4%, 70 of 77 lesions showed complete cure (90.9% efficacy). In the patients who received Lip-AmB 0.4% alone, 36 of 39 lesions showed complete cure (92.3% efficacy). In the patients who received standard treatment alone, 33 of 68 lesions showed complete cure (48.5% efficacy).

Discussion

The current study was completed during the period that antimoniate derivatives (Glucantime/Pentostam) were not easily available in the Islamic Republic of Iran, partly due to the economic sanctions. Generous support from DNDi enabled formulation and production of Lip-AmB under good manufacturing practice conditions, and the topical formulation was tested first in animal models and then its safety was checked in healthy volunteers (15–17). The results of current study showed an acceptable efficacy and tolerable safety profile for Lip-AmB 0.4% alone and in combination with meglumine antimonate for treatment of cutaneous leishmaniasis lesions caused by L. major.

Cutaneous leishmaniasis is a major public health threat in some endemic areas, with 600 000 to 1 million new cases worldwide annually (1, 2). Various treatments have been used for cutaneous leishmaniasis. Antimoniate derivatives, the costly WHO-recommended treatment for cutaneous leishmaniasis, require multiple long-term injections, are accompanied by adverse effects and are not always effective, making treatment of cutaneous leishmaniasis a challenge in developing and developed regions (5,6,19,23). Accordingly, alternative treatments, especially topical formulations, are desired by patients, physicians and governments. Different topical formulations, mainly paromomycin formulations, have shown promising results in preclinical and clinical studies and are marketed (21–24).

Amphotericin B is an antifungal agent and second-line treatment for cutaneous leishmaniasis, visceral leishmaniasis and mucocutaneous leishmaniasis, but is associated with severe toxicity (25). Although Lip-AmB (Ambisome) has limited toxicity and has improved the efficacy of amphotericin B for treatment of visceral leishmaniasis, its application in treatment of cutaneous leishmaniasis is limited due to variable efficacy in different geographical areas, high cost and limited access (26–28). Conventional topical formulations of amphotericin did not show acceptable efficacy, mainly due to the high molecular weight and amphipathic nature of amphotericin, which limits skin penetration (29, 30). The epidermis is the outer layer of the skin and the main barrier to cutaneous absorption of drugs (31, 32). An ideal topical drug delivery system for the treatment of cutaneous leishmaniasis should have enough penetration to reach the dermis, where Leishmania parasites reside (33). The advantages of nanocarriers for cutaneous drug delivery are under investigation (34). The advantages of using liposomes as

nanodelivery systems include greater skin penetration, controlled drug release, drug deposition and targeting in skin layers, lower systemic absorption, and limited adverse effects in transdermal delivery (35).

Previously, the same group have developed several topical liposomal drugs, including amphotericin B. The characteristics of these topical liposomal formulations, including stability, diffusion and efficacy have been investigated in vitro and in vivo. Different concentrations of topical Lip-AmB (0.1, 0.2 and 0.4%) were checked in vitro and in vivo against a few Leishmania species in comparison with Fungizone (micellar formulation) in vitro [15]. Accordingly, it seems that Lip-AmB 0.4% is a promising formulation for treatment of cutaneous leishmaniasis. Lip-AmB 0.4%, with a size ~100 nm, has received a US patent and is produced according to good manufacturing practice guidelines. An irritancy potential test (Draize test) revealed that Lip-AmB 0.4% is safe in animal models (16). In a double-blind, randomized, phase 1 clinical trial, the safety of Lip-AmB 0.4% and its vehicle was evaluated in 27 healthy human volunteers. The healthy volunteers applied Lip-AmB 0.4% and its vehicle twice a day for 1 week or 3 times a day for 2 weeks. In 7 of the volunteers, no skin reactions (including pruritus, burning, skin redness, oedema and scaling) were seen and no significant differences in biophysical characteristics of the skin were observed between Lip-AmB 0.4% and its vehicle. Local skin reactions were observed in some of the remaining 20 volunteers that resulted in withdrawal of 2 of the volunteers (17).

Conclusion

Lip-AmB 0.4% alone or combination with national standard treatment showed acceptable efficacy and safety for treatment of cutaneous leishmaniasis lesions caused by L. major and warrants further investigation in phase 3 clinical trials.

Finding: None.

Competing interests: None declared.

Étude pilote sur l'innocuité et l'efficacité de l'amphotéricine B liposomale topique pour le traitement de la leishmaniose cutanée causée par Leishmania major en République islamique d'Iran

Résumé

Contexte: Les nanoliposomes topiques contenant 0,4 % d'amphotéricine B ont montré des

résultats prometteurs en termes d'innocuité lors d'essais précliniques et cliniques de phase 1 chez des volontaires en bonne santé.

Objectifs : Évaluer l'innocuité et l'efficacité de l'amphotéricine B à 0,4 % chez les patients atteints de leishmaniose cutanée.

Méthodes : Quatorze patients présentant un total de 84 lésions se sont vu administrer le traitement standard national constitué d'injections intralésionnelles d'antimoniate de méglumine hebdomadaire avec cryothérapie bihebdomadaire, ou d'antimoniate de méglumine intramusculaire de manière quotidienne (20 mg/kg/jour pendant 14 jours), et d'amphotéricine B topique à 0,4 % deux fois par jour pendant 28 jours. Vingt-deux patients présentant un total de 46 lésions (sept au maximum) ont été traités seulement par amphotéricine B topique à 0,4 % deux fois par jour pendant 28 jours. Trente patients présentant au total 68 lésions ont reçu le traitement standard national d'antimoniate de méglumine intralésionnel chaque semaine (pour blanchir le pourtour de la lésion) et de cryothérapie bihebdomadaire.

Résultats : Soixante-six patients présentant des lésions de leishmaniose cutanée ont terminé l'étude. Dans l'évaluation de l'innocuité, deux des 36 patients évalués ont signalé une sensation de brûlure tolérable et ont préféré poursuivre le traitement. Douze (92 %) des 14 patients présentant 84 lésions qui ont reçu le traitement standard national associé à l'amphotéricine B à 0,4 % ont terminé l'étude avec une guérison complète. Chez l'un des patients présentant quatre lésions, on a observé une guérison complète pour une lésion et une guérison partielle pour trois lésions. Parmi les 22 patients présentant 46 lésions qui ont reçu uniquement de l'amphotéricine B topique à 0,4 %, 19 ont terminé l'étude et 18 ont montré une guérison complète (efficacité à 95 %). Chez les 30 patients ayant reçu le traitement standard national seul, 33 lésions chez 15 patients ont présenté une guérison complète (48,5 %) au 42ème jour de suivi.

Conclusion : L'amphotéricine B à 0,4 % seule ou en association avec le traitement standard national est sans risque et présente un taux d'efficacité élevé. Elle mérite donc d'être étudiée de manière plus approfondie lors des essais cliniques de phase 3.

WHO EMRO | Pilot study of safety and efficacy of topical liposomal amphotericin B for cutaneous leishm

فرزانه أفشاري، حسين مرتضوی، علي رضا فيروز

الخلاصة

: أظهر الاستخدام الموضعي لنانو ليبوسومال الذي يحتوي على الأمفوتريسين Bالخلفية
بتركيز 0.4 % (0.4 AmB-Lip %) نتائج سلامة واعدة في التجارب السريرية في المرحلة قبل
السريرية والمرحلة الأولى على المتطوعين الأصحاء .

: هدفت هذه الدراسة الى تقييم سلامة وفاعلية نانو ليبوسومال الذي يحتوي علىالأهداف
الأمفوتريسين B بتركيز 0.4 % (0.4 AmB-Lip %) عند استخدامه مع مرضى داء الليشمانيات
الجلدي .

: تلقى أربعة عشر مريضًا يعانون إجمالًا من 84 آفةً العلاجَ الوطني المعياري،طرق البحث
الذي يتمثل في إعطاء ميجلومين أنتيمونيات في الآفة أسبوعيًّا مع العلاج بالتبريد
مرتين أسبوعيًّا، أو علاجًا يوميًّا بالحقن بميجلومين أنتيمونيات في العضل (20 ملجم /
كجم / يوميًّا لمدة 14 يومًا) ، وعلاج موضعي باستخدام نانو ليبوسومال الذي يحتوي على
الأمفوتريسين B بتركيز 0.4% مرتين يوميًّا لمدة 28 يومًا . وتلقى اثنان وعشرون مريضًا
يعانون إجمالًا من 46 آفة (7 على الأكثر) دواء نانو ليبوسومال الذي يحتوي على
الأمفوتريسين B بتركيز 0.4% (0.4 AmB-Lip %) الموضعي وحده مرتين يوميًّا لمدة 28
يومًا . وتلقى ثلاثون مريضًا يعانون إجمالًا من 68 آفةً العلاجَ الوطني المعياري، وهو
العلاج بميجلومين أنتيمونيات داخل الآفة أسبوعيًّا (لتبييض الجلد حول الآفة) والعلاج
بالتبريد مرتين أسبوعيًّا .

: أتم المشاركة في الدراسة ستة وستون مريضًا مصابًا بداء الليشمانيات الجلدي .النتائج
وفي تقييم السلامة، أبلغ مريضان من بين 36 مريضًا خضعوا للتقييم عن شعور بحرقة يمكن
تحملها، وفضَّلا مواصلة العلاج . وأتم الدراسةَ اثنا عشر (92%) مريضًا، من بين 14
مريضًا يعانون من 84 تقرُّحًا، وحصلوا على العلاج الوطني القياسي، بالإضافة إلى نانو
ليبوسومال الذي يحتوي على الأمفوتريسين B بتركيز 0.4% ، وقد تحقق لهم الشفاء تامًا .
وأحد المرضى، الذين كانوا يعانون من 4 آفات، تحقق له الشفاء التام من آفة واحدة
والشفاء الجزئي من ثلاث آفات . ومن بين 22 مريضًا يعانون من 46 آفة وتلقوا فقط نانو
ليبوسومال الذي يحتوي على الأمفوتريسين B بتركيز 0.4% موضعيًّا، أكمل 19 مريضًا
الدراسة، وشُفي 18 منهم تمامًا (بفاعلية تبلغ 95%). أما المرضى الذين تلقوا العلاج
الوطني القياسي فقط وعددهم 30 ، فقد شُفيت 33 آفة لدى 15 مريضًا منهم شفاء تامًّا
(48.5%) عند المتابعة في اليوم 42.

: استخدام نانو ليبوسومال الذي يحتوي على الأمفوتريسين B بتركيز 0.4% (الاستنتاجات%
ويستحق ،عالية بفاعلية ويتميز نِآم الوطني القياسي العلاج مع أو ،وحدة Lip-AmB 0.4)

9 / 14

WHO EMRO | Pilot study of safety and efficacy of topical liposomal amphotericin B for cutaneous leishm

إجراء مزيد من الاستقصاء عليه في تجارب سريرية من المرحلة الثالثة.

References

1. The Global Health Observatory. Explore a world of health data. Leishmaniasis [website]. Geneva: World Health Organization (https://www.who.int/data/gho/data/themes/topics/topic-details/GHO/leishmaniasis#:~:text=The%20disease%20mainly%20affects%20poor,endemic%20for%20leishmaniasis%20in%202019, accessed 18 June 2022).

2. Reithinger R, Dujardin J-C, Louzir H, Pirmez C, Alexander B, Brooker S. Cutaneous leishmaniasis. Lancet Infect Dis. 2007 Sep;7(9):581–96. https://doi.org/10.1016/S1473-3099(07)70209-8

3. Gonzalez U, Pinart M, Reveiz L, Alvar J. Interventions for Old World cutaneous leishmaniasis. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD005067. https://doi.org/10.1002/14651858.CD005067.pub3 PMID:18843677

4. Khatami A, Emmelin M, Talaee R, Miramin-Mohammadi A, Aghazadeh N, Firooz A, et al. Lived experiences of patients suffering from acute Old World cutaneous Leishmaniasis: a qualitative content analysis study from Iran. J Arthropod Borne Dis. 2018 Jun 13;12(2):180–95. PMID:30123812

5. Kashani MN, Firooz A, Eskandari SE, Ghoorchi MH, Khamesipour A, Khatami A, et al. Evaluation of meglumine antimoniate effects on liver, kidney and pancreas function tests in patients with cutaneous leishmaniasis. Eur J Dermat. 2007. Nov–Dec 2007;17(6):513–5. https://doi.org/10.1684/ejd.2007.0266 PMID:17951131

6. Khatami A, Firooz A, Gorouhi F, Dowlati Y. Treatment of acute Old World cutaneous leishmaniasis: a systematic review of the randomized controlled trials. J Am Acad Dermatol. 2007 Aug;57(2):335.e1–29. https://doi.org/10.1016/j.jaad.2007.01.016 PMID:17337090

7. Nassiri-Kashani M, Firooz A, Khamesipour A, Mojtahed F, Nilforoushzadeh M, Hejazi H, et al.

10 / 14

A randomized, double-blind, placebo-controlled clinical trial of itraconazole in the treatment of cutaneous leishmaniasis. J Eur Acad Dermatol Venereol. 2005 Jan;19(1):80–3. https://doi.org/10.1111/j.1468-3083.2004.01133.x PMID:15649196

8. Jaafari MR, Bavarsad N, Bazzaz BSF, Samiei A, Soroush D, Ghorbani S, et al. Effect of topical liposomes containing paromomycin sulfate in the course of Leishmania major infection in susceptible BALB/c mice. Antimicrob Agents Chemother. 2009 Jun;53(6):2259–65. https://doi.org/10.1128/AAC.01319-08 PMID:19223613

9. Shazad B, Abbaszadeh B, Khamesipour A. Comparison of topical paromomycin sulfate (twice/day) with intralesional meglumine antimoniate for the treatment of cutaneous leishmaniasis caused by L. major. Eur J Dermatol. Mar–Apr 2005;15(2):85–7. PMID:15757817

10. Firooz A, Khamesipour A, Ghoorchi MH, Nassiri-Kashani M, Eskandari SE, Khatami A, et al. Imiquimod in combination with meglumine antimoniate for cutaneous leishmaniasis: a randomized assessor-blind controlled trial. Arch Dermatol. 2006 Dec;142(12):1575–9. https://doi.org/10.1001/archderm.142.12.1575 PMID:17178983

11. Laniado-Laborín R, Cabrales-Vargas MN. Amphotericin B: side effects and toxicity. Rev Iberoam Micol. 2009 Dec 31;26(4):223–7. https://doi.org/10.1016/j.riam.2009.06.003 PMID:19836985

12. Wortmann G, Zapor M, Ressner R, Fraser S, Hartzell J, Pierson J, et al. Lipsosomal amphotericin B for treatment of cutaneous leishmaniasis. Am J Trop Med Hyg. 2010 Nov;83(5):1028–33. https://doi.org/10.4269/ajtmh.2010.10-0171 PMID:21036832

13. Zylberberg C, Matosevic S. Pharmaceutical liposomal drug delivery: a review of new delivery systems and a look at the regulatory landscape. Drug Deliv. 2016;23(9):3319–29. https://doi.org/10.1080/10717544.2016.1177136

14. Prajapati BG, Patel NK, Panchal MM, Patel RP. Topical liposomes in drug delivery: a review. IJPRT. 2012 Jan–Jun;4(1):39–44. https://doi.org/10.1016/0169-409X(90)90021-J

15. Jaafari MR, Hatamipour M, Alavizadeh SH, Abbasi A, Saberi Z, Rafati S, et al. Development of a topical liposomal formulation of Amphotericin B for the treatment of cutaneous leishmaniasis. Int J Parasitol Drugs Drug Resist. 2019 Dec;11:156–65. https://doi.org/10.1016/j.ijpddr.2019.09.004 PMID:31582344

16. Eskandari SE, Firooz A, Nassiri-Kashani M, Jaafari MR, Javadi A, Miramin-Mohammadi A, et al. Safety evaluation of nano-liposomal formulation of amphotericin B (sina ampholeish) in animal model as a candidate for treatment of cutaneous leishmaniasis. J Arthropod Borne Dis. 2018 Sep 30;12(3):269–75. PMID:30584550

17. Eskandari SE, Firooz A, Nassiri-Kashani M, Jaafari MR, Javadi A, Mohammadi AM, et al. Safety evaluation of topical application of nano-liposomal form of amphotericin B (SinaAmpholeish) on healthy volunteers: phase I clinical trial. Iran J Parasitol. 2019 Apr–Jun;14(2):197–203. PMID:31543907

18. Layegh P, Rajabi O, Jafari MR, Malekshah PET, Moghiman T, Ashraf H, et al. Efficacy of topical liposomal amphotericin B versus intralesional meglumine antimoniate (Glucantime) in the treatment of cutaneous leishmaniasis. J Parasitol Res. 2011;2011:656523. https://doi.org/10.1155/2011/656523 PMID:22174993

19. Oliveira LF, Schubach AO, Martins MM, Passos SL, Oliveira RV, Marzochi MC, et al. Systematic review of the adverse effects of cutaneous leishmaniasis treatment in the New World. Acta Trop. 2011 May;118(2):87–96. https://doi.org/10.1016/j.actatropica.2011.02.007 PMID:21420925

20. Masmoudi A, Maalej N, Mseddi M, Souissi A, Turki H, Boudaya S, et al. [Glucantime injection: benefit versus toxicity] (in French). Med Mal Infect. 2005 Jan;35(1):42–5. https://doi.org/10.1016/j.medmal.2004.07.032 PMID:15695033

21. Belazzoug S, Neal RA. Failure of meglumine antimoniate to cure cutaneous lesions due to Leishmania major in Algeria. Trans R Soc Trop Med Hyg. 1986;80(4):670–1. https://doi.org/10.1016/0035-9203(86)90176-8 PMID:3544363

22. Hadighi R, Mohebali M, Boucher P, Hajjaran H, Khamesipour A, Ouellette M, et al. Unresponsiveness to Glucantime treatment in Iranian cutaneous leishmaniasis due to drug-resistant Leishmania tropica parasites. PLoS Med. 2006 May;3(5):e162. https://doi.org/10.1371/journal.pmed.0030162 PMID:16605301

23. Azim M, Khan SA, Ullah S, Ullah S, Anjum SI, et al. Therapeutic advances in the topical treatment of cutaneous leishmaniasis: a review. PLoS Negl Trop Dis. 2021 Mar 3;15(3):e0009099. https://doi.org/10.1371/journal.pntd.0009099 PMID:33657097

24. Shirzadi MR. Lipsosomal amphotericin B: a review of its properties, function, and use for treatment of cutaneous leishmaniasis. Res Rep Trop Med. 2019 Apr 26;10:11–8. https://doi.org/10.2147/RRTM.S200218 PMID:31118866

25. Minodier P, Retornaz K, Horelt A, Garnier J-M. Liposomal amphotericin B in the treatment of visceral leishmaniasis in immunocompetent patients. Fundam Clin Pharmacol. 2003 Apr;17(2):183–8. https://doi.org/10.1046/j.1472-8206.2003.00168.x PMID:12667228

26. Sinha PK, Roddy P, Palma PP, Kociejowski A, Lima MA, Das VNR, et al. Effectiveness and safety of liposomal amphotericin B for visceral leishmaniasis under routine program conditions in Bihar, India. Am J Trop Med Hyg. 2010 Aug;83(2):357–64. https://doi.org/10.4269/ajtmh.2010.10-0156 PMID:20682882

27. Ritmeijer K, ter Horst R, Chane S, Aderie EM, PieningT, Collin SM, et al. Limited effectiveness of high-dose liposomal amphotericin B (AmBisome) for treatment of visceral leishmaniasis in an Ethiopian population with high HIV prevalence. Clin Infect Dis. 2011 Dec;53(12):e152–8. https://doi.org/10.1093/cid/cir674 PMID:22016502

28. El-On J, Jacobs GP, Witztum E, Greenblatt CL. Development of topical treatment for cutaneous leishmaniasis caused by Leishmania major in experimental animals. Antimicrob Agents Chemother. 1984 Nov;26(5):745–51. https://doi.org/10.1128/AAC.26.5.745 PMID:6517557

29. Perez AP, Altube MJ, Schilrreff P, Apezteguia G, Celes FS, Zacchino S, et al. Topical amphotericin B in ultradeformable liposomes: formulation, skin penetration study, antifungal and antileishmanial activity in vitro. Colloids Surf B Biointerfaces. 2016 Mar 1;139:190–8. https://doi.org/10.1016/j.colsurfb.2015.12.003 PMID:26709977

30. Moser K, Kriwet K, Naik A, Kalia YN, Guy RH. Passive skin penetration enhancement and its quantification in vitro. Eur J Pharm Biopharm. 2001 Sep;52(2):103–12. https://doi.org/10.1016/s0939-6411(01)00166-7 PMID:11522474

31. Proksch E, Brandner JM, Jensen J. The skin: an indispensable barrier. Exp Dermatol. 2008 Dec;17(12):1063–72. https://doi.org/10.1111/j.1600-0625.2008.00786.x PMID:19043850

32. Carneiro G, Aguiar MG, Fernandes AP, Ferreira LAM. Drug delivery systems for the topical treatment of cutaneous leishmaniasis. Expert Opin Drug Deliv. 2012 Sep;9(9):1083–97. https://doi.org/10.1517/17425247.2012.701204 PMID:22724539

33. Patzelt A, Mak WC, Jung S, Knorr F, Meinke MC, Richter H, et al. Do nanoparticles have a future in dermal drug delivery? J Control Release. 2017 Jan 28;246:174–82. https://doi.org/10.1016/j.jconrel.2016.09.015 PMID:27641832

34. Maghraby GME, Williams AC, Barry BW. Can drug-bearing liposomes penetrate intact skin? J Pharm Pharmacol. 2006 Apr;58(4):415–29. https://doi.org/10.1211/jpp.58.4.0001 PMID:16597359

35. Maghraby, G.M.E., A.C. Williams, and B.W. Barry, Can drug--bearing liposomes penetrate intact skin? Journal of Pharmacy and Pharmacology, 2006. 58(4): p. 415-429.

Thursday 11th of July 2024 08:02:54 AM