ORIGINAL REPORT

Comparison of Intralesional Sodium Stibogluconate versus Intralesional Meglumine Antimoniate for the Treatment of *Leishmania major* Cutaneous Leishmaniasis

Michal SOLOMON[1,2], Ayelet OLLECH[1,2], Felix PAVLOTSKY[1,2], Aviv BARZILAI[1,2], Eli SCHWARTZ[2,3], Sharon BAUM[1,2] and Nadav ASTMAN[1,2]

[1]Department of Dermatology and [3]Center for Geographic Medicine and Tropical Diseases, Chaim Sheba Medical Center, Tel Hashomer, and [2]The School of Medicine, Tel Aviv University, Tel Aviv, Israel

Israel is endemic for Old-World cutaneous leishmaniasis. The most common species is *Leishmania major*. However, the available treatment options are limited. This study's objective was to compare the authors' experience with different antimony intralesional treatments of *Leishmania major* cutaneous leishmaniasis. A retrospective evaluation was undertaken for cases of *Leishmania major* cutaneous leishmaniasis treated by pentavalent antimony in a university-affiliated medical centre in Israel. The previous treatment of intralesional sodium stibogluconate (Pentostam®) was compared with the current treatment of meglumine antimoniate (Glucantime®). One hundred cases of cutaneous leishmaniasis were treated during the study period, of whom 33 were treated with intralesional sodium stibogluconate and 67 were treated with intralesional meglumine antimoniate. The patients were 78 males and 22 females, mean age 24 (range 10–67) and there was a total of 354 skin lesions. Within 3 months from treatment, 91% (30/33) of the intralesional sodium stibogluconate group and 88% (59/67) of the intralesional meglumine antimoniate group had complete healing of the cutaneous lesions after an average of 3 treatment cycles (non-statistically significant). In conclusion, the 2 different medications have the same efficacy and safety for treating cutaneous leishmaniasis. Pentavalent antimoniate intralesional infiltration treatment is safe, effective, and well tolerated with minimal side effects for Old-World cutaneous leishmaniasis.

Key words: leishmaniasis; *Leishmania major*; *Leishmania Tropica*; pentavalent antimoniate; intralesional.

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Corr: Michal Solomon MD, Department of Dermatology, The Chaim Sheba Medical Center, Tel Hashomer, 52621 Israel. E-mail: solomondr1@gmail.com

SIGNIFICANCE

Israel is endemic for Old-World cutaneous leishmaniasis. The most common species is *Leishmania major*. We compared our experience with different antimony intralesional treatments of *Leishmania major* cutaneous leishmaniasis. Intralesional sodium stibogluconate (Pentostam®) was compared with meglumine antimoniate (Glucantime®). In total, 91% and 88% of the patients had complete healing of the cutaneous lesions after an average of 3 treatment cycles. The two different medications have the same efficacy and safety for treating cutaneous leishmaniasis.

Old world cutaneous leishmaniasis (CL) is endemic in Israel and is caused mainly by *Leishmania major* and *Leishmania tropica* (1), and recently by *L. infantum* as well (2). *L. major* CL is usually a benign disease and is limited to the skin. Despite its benign nature, it can still lead to disfigurement. Therefore, prompt and effective treatment is necessary to prevent cosmetic flaws. The choice of treatment should be based on the specific parasite species and the patient's individual characteristics, such as disease severity, immune status, and comorbidities. Pentavalent antimony remains the first line of treatment for all disease forms (3). According to US policy, intravenously administered sodium stibogluconate (IV SSG; Pentostam) is considered to be the drug of choice for treating CL. However, systemic SSG treatment is associated with a high rate of significant adverse events and necessitates prolonged hospitalisation (4). As a result, topical therapy has emerged as an attractive treatment option for CL when systemic therapy is not needed. The intralesional injection of pentavalent antimony (IL PA) derivatives directly into the lesion has been described for about 40 years and was recently included in the recommendations produced by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH) for CL treatment (4). In the past, IL SSG was used for treating CL in the Anglophile world and IL MA was used in the Francophile world. In Israel the available medicine was IL SSG, but due to a halt in production in 2020, we began to use IL MA.

Our objective in conducting this study was to assess the efficacy of IL PA for treating exclusively *L. major* CL and to compare two types of antimony treatments: IL sodium stibogluconate (IL SSG) versus IL meglumine antimoniate (IL MA). To the best of our knowledge, no such comparison has been made before.

PATIENTS AND METHODS

We retrospectively evaluated all cases of *L. major* CL that were referred to the dermatology clinic and the centre of geographic medicine at Sheba Medical Centre between October 2004 and October 2006 and which were treated with IL SSG (5), comparing those cases with all cases of CL that were treated with IL MA between October 2020 and May 2021.

CL was diagnosed by direct smear or by skin biopsy. Because it had become the standard diagnostic procedure, polymerase chain reaction (PCR) testing was performed in most of the more recent cases (6). Previously, PCR was done only on a convenient sample to map the endemic regions according to the species of leishmania. IL PA treatment was given in an outpatient setting. The indications were a limited disease (i.e. <5 lesions), or the failure of previous topical treatment. The medication was injected until the entire lesion had blanched (up to 0.5 cc [50 mg] per ulcer). The treatment was repeated every 3–4 weeks until the lesion had become flattened with either complete re-epithelization or reduction of the lesion to less than 3 mm.

Clinical cure was defined as complete re-epithelization or flattening of skin lesions, or as reduction of the lesion to less than 3 mm, within 3 months after treatment and without relapse of ulcers. Treatment failure was defined as failure to achieve cure within 3 months of the last IL dose. In addition, any patient who was clinically cured but had a relapse during the follow-up period was also considered to have "failed" treatment. Fisher's exact test (two-tailed) was used to compute the *p*-value in the prevalence assessment. A p-value <0.05 was considered significant. The study was approved by the institutional review board (protocol approval no. 7274-09).

RESULTS

The IL SSG (Pentostam) group consisted of 33 patients (27 males and 6 females), most of whom were Israeli military personnel (**Table I**). Their mean age ± SD at diagnosis was 23 ± 9.05 years (median 20, range 5–50). The average period from diagnosis to the initiation of IL SSG treatment was 2.5 months. These patients had a mean of 3 cutaneous lesions and a total of 93 lesions that were treated by an average number of 2.5 injections (range: 1–6). In total, 30 out of 33 patients (91%) were cured of CL within 3 months of treatment initiation. Side effects were mild and consisted of pain at the injection site, with 2 patients experiencing a transient local reaction.

The second group consisted of 67 patients, also mainly Israeli military personnel (51 males and 16 females), who were treated for CL with IL MA (Glucontime) (see Table I). Their mean age ± SD at diagnosis was 25.2 ± 11.8 years (median 20, range 10–67) and the CL was caused by *L. major* detected by PCR in 47 out of 57 of the cases. The remaining cases were from an endemic region of *L. major* in Israel (southern Israel). The mean number of lesions among these patients was 4, and a total of 261 lesions were treated. The average time between diagnosis and initiation of IV SSG treatment was 2.8 months. Complete healing of cutaneous lesions was observed in 59 (88%) cases within 3 months of IL MA initiation. Side effects were mild and consisted of pain at the site of injection.

DISCUSSION

Cutaneous leishmaniasis (CL) is a chronic and potentially debilitating disease that can have cosmetic consequences, yet there is no consensus on the optimal treatment modality for this condition. The aim of our present study was to assess the efficacy of IL PA drugs for CL treatment. This retrospective study exclusively addressed infections caused by *L. major* CL. The results of our present study showed a high cure rate for the 2 different regimens of IL PA treatment: approximately 90% of our patients achieved a complete cure within 3 months. These results are superior to the 74–82% clearance achieved by paromomycin ointment treatment, which is primarily used for *L. major* (7–9). We administered injections (IL MA and IL SSG) to our patients at 3-week intervals and obtained better outcomes compared with other studies that injected IL SSG every week (10). Pentavalent antimony compounds administered parenterally are the mainstays of CL treatment in several regions in the world, despite their recognized toxicity, which requires frequent laboratory monitoring (10). As a result of these drawbacks, the WHO Expert Committee on leishmaniasis has expanded the recommendations for the use of local therapies, including intralesional infiltration of pentavalent antimony as CL therapy alternatives (10). Administering pentavalent antimony via the IL route is an attractive option, thanks to the lower total doses of antimony used (and thus fewer toxic effects) and a more flexible schedule without the requirement for daily drug administration (10).

Table I. Comparison of patients treated with intralesional (IL) sodium stibogluconate (SSG) versus IL meglumine antimoniate (MA) treatment

Factor	IL SSG Patients ($n=33$)	IV MA Patients ($n=67$)	p-value
Mean age, years (range)	23 (5–50)	25 (10–67)	NS
Median age, years	20	20	NS
Gender % male	27M/6F 81.8%	51M/16F 76.1%	NS
*PCR testing, N (%)	3 (9%)	47 (70%)	0.0001
Time lag to treatment (range)	2.5 months (1–6)	2.8 months (1–7)	NS
Mean number of lesions (range)	3 (1–6)	4 (1–15)	NS
Total number of lesions	93	261	
Failure of prior paromomycin ointment topical treatment, N (%)	7 (21%)	11 (16%)	NS
No. of IL treatments	2.5 sessions (range 1–6)	2 sessions (range 1–4)	NS
Cure rate	91%	88%	NS

NS: not statistically significant.
*PCR was done only in a convenient sample because all the cases were from an endemic area for *Leishmania major* in Israel.

While sodium stibogluconate and meglumine antimoniate are two widely used antimonial drugs, the relative effectiveness of intralesional MA and SSG therapies in the treatment of *L. major* CL is unclear, as previous studies usually lumped all Old-World species together. Nowadays, with PCR for specious specific diagnosis widely available, we can conduct studies evaluating the efficacy of IL PA for each species separately. In fact, in Israel we demonstrated that *L. tropica* is more resistant to topical therapy than *L. major* (11).

For example, a randomized comparative study of 96 patients was conducted in Iran in which the principal pathogenic species were *L. major* and *L. tropica* (12). This study demonstrated that intralesional meglumine antimoniate resulted in complete recovery in only 41.7% of patients, whereas topical paromomycin produced an even lower cure rate of 16.6% ($p<0.05$). The authors suggested that their study's more stringent criteria for healing might have contributed to the lower recovery rates, while ignoring the possibility that the inclusion of more resistant species such as *L. tropica* affected their results. Another recent systematic review assessment of the efficacy of IL PA therapy for CL showed that IL SSG and IL MA were effective in the treatment of CL, with cure rates ranging from 47% to 97% for IL SSG and from 70% to 93% for IL MA (10). This wide range of effectiveness might also be due to different species being lumped together in these studies. Additionally, therapeutic regimens varied widely between studies. In the Old-World leishmaniasis studies, the number of infiltrations ranged from 1–16, and the most common interval between the injections was 7 days (5). The high response rate of the treatment in our study can be attributed to the fact that all the cases were caused by *L. major* CL. Furthermore, we treated the patients every 3 weeks and found that there was no need for so many injections. Our study has certain drawbacks, such as being retrospective and lacking a control group for comparison, but its strength is having species-specific results.

The limitations of the study include a small patient sample and the fact that the 2 drugs belong to the same pharmaceutical group of pentavalent antimonials.

In conclusion, our study, which exclusively addressed infections caused by *L. major* CL, showed that IL-SSG and IL-MA cure rates were equally high (approximately 90%) and had minimal adverse events. Further studies are needed to confirm the efficacy of IL PA for each CL species.

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