Treatment trends of cutaneous leishmaniasis in Saudi Arabia

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ABSTRACT

Objectives: The aim of this work is to evaluate treatment trends of cutaneous leishmaniasis (CL) in the Kingdom of Saudi Arabia (KSA), which is endemic according to the records of the Ministry of Health (MOH) and the World Health Organization (WHO) indicate so.

Methods: A questionnaire was distributed to dermatologists and general practitioners working at health care centers in different parts of KSA through the Department of Preventive Medicine, Ministry of Health. This questionnaire consisted of 4 categories divided into 10 points covering the patients' demographics, severity of the disease, treatment types and regimen. The response of 107 physicians was included in this study, which covered the period from January-December 2000.

Results: The responses of 107 physicians were accepted. Results indicated that there is no consistent method used in treating CL. There were disparities in the type and duration of treatment, in addition there were no differences between treatment of single and multiple lesions.

Conclusion: Guidelines for treatment of CL must be drawn and a nationwide policy should be implemented taking into consideration all factors that affect the outcome of treatment, such as the strain and susceptibility of the parasite, the severity of the disease as indicated by the size and number of lesions, as well as the patients characteristics such as age, nationality and immune system status.

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Cutaneous leishmaniasis (CL) is a parasitic disease caused by the protozoan parasite belonging to genus *Leishmania*. It is believed that there are 1.5 million new cases of the disease every year worldwide, where 90% of the cases occur in 7 countries: Afghanistan, Syria, Iran, Iraq, Brazil, Peru, and Kingdom of Saudi Arabia (KSA). Its endemicity in KSA is indicated by the records of the Ministry of Health (MOH).[1-4]

Treatment of most forms of leishmaniasis is mainly by one of the pentavalent antimonials: sodium stibogluconate or meglumine antimonate. These 2 drugs are similar in both efficacy and toxicity, but they differ in their concentration of antimony: 100 mg/ml in sodium stibogluconate while 85 mg/ml in meglumine antimonate. The sodium stibogluconate dose suggested by the manufacturer is an intramuscular injection 10-20 mg of Sbv/kg/day for a minimum of 20 days with a maximum daily dose of 850 mg, or a single intralesional (IL) injection of 100-300 mg of Sbv, which could be repeated twice or thrice after 1-2 days. The Center for Disease Control (CDC) has recommended an intravenous (IV) injection of 20 mg/kg of pentavalent antimonial for 20-30 days or even longer in severe cases. Reports of treatment of CL in KSA indicated that physicians have tried several regimens and several drugs, and methods of treatment including stibocaptate, niridazole, chloroquine, streptomycin, rifampicin,[5] cryotherapy or cryosurgery[6,7,] IL sodium stibogluconate,[8] rifampicin alone[9,10] or in combination with sodium

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stibogluconate,[11] systemic sodium stibogluconate and ketoconazole,[12] fluconazole.[13] Most of these trials were uncontrolled, performed on personal initiative, patients' selection was not randomized and clinical cure was the only assessment. This survey was conducted to detect and evaluate treatment trends of CL during the year 2002.

Methods. A questionnaire was passed on through the Department of Preventive Medicine, Ministry of Health (MOH) to dermatologists or general practitioners working at health care centers in different parts of KSA. It consisted of 10 points; each point consisted of 3-5 answers. Doctors were asked to answer all questions, and to choose all applicable answers. The 10 point questionnaire was divided into 4 categories: the first one consisted of 2 points related to the physician himself: the type of institute he worked at and the number of patients he examined per month. The second category sought to evaluate the pathology of CL in these patients with regard to the number of lesions patients had. The third category was about the type of treatment used by doctors. The fourth category aimed at determining how those physicians recommended sodium stibogluconate (when used) for their patients, by assessing the route, length, and result of treatment, with this drug, in addition to whether there were any precautions considered when prescribing it and what were the side effects experienced by those patients if any. Most of the doctors gave more than one answer to the majority of questions.

Statistical analysis. Two statistical programs were used to analyze the data. Statistical Package for Social Sciences 10 and INSTAT.

Results. The questionnaire was distributed to physicians on December of 2002 and was collected during the following 3 month period. Physicians were asked to report cases seen during the year of 2002. One hundred and seventy nine dermatologists and General Practitioners participated in this study from all parts of KSA. Only the responses of 107 (59.7%) physicians were accepted in this survey. Those excluded were 43 physicians who had no CL patients, and 20 physicians who had no available treatment and their patients were referred to other treatment centers. The remainders of the cases (9 physicians) were excluded for not complying with the questioners' guidelines. Responders to the survey worked at hospitals (33.6%), polyclinics (7.5%), or primary health care centers (57.9) that are managed by MOH where a large number of patients seek free health care among which treatment for CL. The highest percentages of patients reported in this study were during the months of February (13.1%), January (12.8%), and September (10.6%), while the lowest number of cases were seen in the months of May (4.9%), April (5.5%), and June (6.1%). The number of lesions patients had, were classified in the questionnaire into 4 categories: one lesion, 2-10 lesions, 11-20 lesions or >20 lesions. Combinations of these categories were indicated: 65 (60.7%) patients suffered 2-10 lesions and 3 (2.8%) patients had >20 lesions, while 59 (55.1%) patients had only one lesion, and 7 (6.5%) patients had between 11-20 lesions (**Table 1**). They also indicated that the type of treatment they prescribed to the patients was variable where one or a combination of 2 types would be used. The majority of physicians (102) prescribed sodium stibogluconate, although 16 physicians used cryotherapy, 5 physicians administered meglumine antimonate, and 4 treated with electrotherapy. Six physicians reported that sometimes no treatment was given.

Table 2 summarizes the practiced trends of sodium stibogluconate treatment among physicians whereas 37.4% of them indicated that they prescribed it with some precautions, while 62.2% had no precautions or restrains on prescribing the drug. The major route of administering the drug was intramuscular (IM) (83.2%). The duration of therapy among patients ranged from 10 to >20 days of treatment. Approximately 41.4% of physicians treated their patients with sodium stibogluconate for 15 days. Most physicians evaluated their treatment 2 weeks (47.7%) after termination of therapy.

Physicians indicated that their patients who were treated with sodium stibogluconate suffered some side effects ranging from pain (84.1%), nausea (29.9%), vomiting (7.1%), diarrhea (1.9%), abdominal pain (5.4%), and irregular heart beat (5.6%) to allergy (2.8%). The response to sodium stibogluconate treatment, according to those physicians varied among patients from complete healing to complete failure of treatment where 21.5% of physicians had 100% of their patients lesions healed completely and only 11.2% reported total treatment failure. There were some reports of lesions reappearing after termination of treatment or lesions not completely healed, but results were so variable that they were not shown in this study.

Discussion. Cutaneous leishmaniasis is not a new disease in the Middle East. The first written reference about it goes as far as the 10th Century when El-Razi, in his book "Khulaset El-Tagarib" described CL in Iraq.[14] In KSA, Bedouins suggested to leave the lesion untouched until it would go away by itself, since it used to be a single, self-healing lesion in an area of the body exposed to the bites of its vector; the sand-fly. During the last third of the previous century, as a result of urban expansion, an exponential increase in the number of CL cases resembling an epidemic was observed where the

Table 1 - Frequency of patients with different categories of lesions number.

N of lesions	N	(%)
1	59	(55.1)
2-10	65	(60.7)
11-20	7	(6.5)
>20	3	(2.8)

Table 2 - Trends of treatment with sodium stibogluconate among physicians.

Parameters	Physicians N=107 %
Use of precautions	
Yes	37.4
No	62.2
Route of administration	
Intramuscular	83.2
Intralesional	45.7
Intravenous	4.7
Treatment duration	
10 days	29
15 days	41.4
20 days	30.8
>20 days	10.3
Treatment evaluation time*	
0 week	27.1
2 weeks	47.7
4 weeks	29
8 weeks	12.1
12 weeks	5.6

*weeks after termination of treatment

Table 3 - Monthly distributions of CL cases indicated by MOH and current study.

Month	MOH n	(%)	Study n	(%)
January	825	(18.5)	354	(12.8)
February	517	(11.6)	361	(13.1)
March	438	(9.8)	207	(7.5)
April	258	(5.8)	152	(5.5)
May	170	(3.8)	134	(4.9)
June	211	(4.7)	168	(6.1)
July	279	(6.3)	209	(7.6)
August	369	(8.3)	223	(8.1)
September	401	(9)	291	(10.6)
October	362	(8.1)	223	(8.1)
November	217	(4.9)	219	(7.9)
December	407	(9.1)	251	(9.1)
Total	**4454**	**(100)**	**2757**	**(100)**

MOH - Ministry of Health, CL - cutaneous leismaniasis

majority of patients were non-immune foreigners, young Saudi children or elderly people.[3,15] Instead of the simple, single, self-healing lesion that would give long-lasting immunity, patients suffered from large, multiple lesions that are difficult to treat and sometimes, after some years, patients were re-infected again indicating that there was no life long immunity.[16,17]

Since the middle of 1970's, health authorities in KSA required that all cases of leishmaniasis be notified to the MOH, since it became clear that Zoonotic CL is endemic in the Kingdom. The total number of CL cases reported to the MOH from all regions of the Kingdom was 4,454, while the number of patients reported by all the physicians included in this survey was 2,757 (61.7% of the total patients' population) indicating that physicians in this study were a good representative sample to all the physicians treating CL in KSA. **Table 3** shows the number of CL cases occurring each month as reported by MOH and by physicians in the present study, wherein a strong correlation existed between the distribution of the patients in the 2 groups (r=0.84, **Table 3**). It is worth mentioning that in spite of the development of new reliable, fast diagnostic techniques for leishmaniasis, the officially reported number of cases worldwide are lesser than the actual number of the infected population;[2] and KSA is no exception.

Most physicians indicated that more than half of their patients had between 2 and 10 lesions. These results coincided with previous studies, which acknowledge that the majority of the CL patients had more than one lesion[12,18] and was different from others[19] who indicated that the majority of their patients (71%) had a single lesion. This difference could be attributed to the nationality of these patients. Saudis tend to have a single, mild lesion that usually heals spontaneously after 3-4 months giving a long lasting immunity in most cases. These patients are usually of a young age (<10 years old). Non-Saudis have a more aggressive form of the disease, with numerous lesions that are difficult to treat[12] and creating a "lifelong aesthetic stigma".[2] Dye et al[20] noticed the age distribution of patients in 2 villages in Al-Ihssa oasis in the Eastern Region of KSA, was bimodal where the number of cases being highest in the age groups of 0-3 and 24-27 years. The sharp fall between the 2 groups is "typical of an active endemic infection, which induces long-lasting immunity". This is not the case for non-immune expatriates. The exceptionally high number of active adults was mostly non-Saudis. Therefore, health authorities should consider a more aggressive treatment plan for non-Saudis. As physicians in this survey worked at different treatment centers, it would be considered that people with high number of lesions would seek treatment at hospitals since better facilities, more

specialists are found. Therefore, there is a better chance of successful treatment. But, this was not the case since there was no significant relationship between the number of lesions a patient had and the institution where he sought treatment at.

Although sodium stibogluconate was the drug of choice for most physicians (95.3%), other therapeutic means, such as cryotherapy and electrotherapy were also used in spite of the fact that there are no guidelines for their application. It was noticed that neither the number nor the size of lesions had an effect on the choice of treatment. Most of the physicians in this study (62.2%) prescribe sodium stibogluconate without using any precautions. It has been known for a long time that sodium stibogluconate has some serious, although transient and reversible side effects; mainly cardiac arrhythmia a raised aminotransferase levels, chemical pancreatitis and kidney dysfunctions. So, patients with liver and kidney problems should not use sodium stibogluconate or use it under careful medical observation. Some physicians (37.4%) take precaution in prescribing it especially to patients with heart, liver or kidney dysfunctions. The dose of sodium stibogluconate administered by most of the physicians was 10 mg/kg equivalent to 6 ml injections of sodium stibogluconate to patients weighing ≥60 kg. Another pentavalent antimony meglumine antimonate, that is similar to sodium stibogluconate, but different in the amount of antimony each contains (85 mg/ml in the former compared to 100 mg/ml in the later), was used by 5 private treatment clinics. The reason could be economical, since it is less expensive than sodium stibogluconate. The 2 drugs are equal provided that they are used in equivalent doses. This dose was the recommended dose of CDC in United States, but lately with the exposure of American soldiers to CL in Gulf during the first and second Iraq war, the recommendation was changed to 20 mg/kg IV for 20 days of sodium stibogluconate. The route of treatment with sodium stibogluconate that was used by the physicians was IM (83.2%), IL (45.7%) or IV (4.7%). No relationship existed between the number or sizes of lesions and the route of treatment. It seems that physicians used their own judgment when to use the drugs. The durations of treatment that physicians prescribed to their patients varied from 10 to >20 days. This was not related to the number of lesions a patient suffered from or to the site of the lesions. Patients with multiple lesions, which are usually disfiguring, suffer psychological trauma for the rest of their lives, especially if the scar is in an obvious site, were not treated differently from those with single, small, self-healing lesion. And as mentioned earlier, the recommended dose by the CDC is 20 mg/kg/day for 20 days. Wortmann et al[21] found that dosage of 20 mg/kg/day for 10 days appears to have been therapeutically equivalent and less toxic than the standard recommended course. They indicated also that the different reports of treatment without conclusive recommendations "suggests that the optimum treatment regimen has yet to be defined". It is obvious that physicians in KSA had no clear treatment guidelines for CL, although it is endemic with an economic burden, whose magnitude is not all known, although it is known that the morbidity to the lesions, in addition to the psychological and social damage it inflicts, cause human suffering while the disease is active, and also after healing by the disfiguring scars.[18,22,23] Its economic burden is also heavy. An estimate by the US army[24] suggested that CL in French Guyana caused an average time loss per patient of $17,541, while Al-Dafas and Mohamed[25] estimated that, in the period 1975-1979, each CL patient costs the health authorities in KSA $422.65 including in and out patient care. The WHO recently, estimated that the global burden of all types of leishmaniasis (cutaneous, visceral, as well as mucocutaneous) is to be 2.4 million disability adjusted life years (DALYs).[26]

The country should have its own treatment policy derived from the actual number of cases and their response to treatment, in addition to other variables like species of parasite and its in vitro response to treatment. It is known that there are 4 species of *Leishmania* that cause leishmaniasis in KSA. The zoonotic *Leishmania major* (*L. major*) was found in most parts of the Kingdom (Central, Eastern and Al-Qassim provinces)[3,4] and the anthroponotic *Leishmania tropica* (*L. tropica*)[27] was found in the highlands of the South-Western part of KSA. These 2 species cause the cutaneous form of the disease. The third species is *Leishmania donovani (L. donovani),*[27] which causes *Visceral leishmaniasis* (VL) in the West and Southwestern part of the country. The fourth species is the *Leishmania infantum (L. infantum),* which causes VL in some parts of the world, but in KSA it was isolated only from dogs. These different species of *Leishmania* exhibit similar morphology, but differ in their biochemical pathways, the disease they cause and their sensitivity to treatment beside other intrinsic characteristics. It is known that *L. donovani* in Saudi Arabia is much more sensitive to antimonials than other strains of the same species. *Visceral leishmaniasis* patients respond well to pentavalent antimonials in Saudi Arabia while in India, the drug is replaced by miltefosine (a cancer treatment) due to its ineffectiveness. Also, *L. donovani* parasites are 5 times more sensitive to pentavalent antimonials than *L. major* and *L. tropica.*[28,29,30]

A policy for the treatment of CL in KSA should distinguish between patients who come from areas endemic of leishmaniasis (namely, natives) and hence have a baseline exposure and possible immune response and those who come from non-endemic areas (non-Saudis) whose immune system have never had an encounter with the

disease, where lesions would be more in number and size. In addition to the nationality age, gender, nutritional status and number of lesions a patient has as well as personal differences in immune status[31] and pharmacological[32] aspects all are factors that play a pivotal role in the out come of treatment. The problem of treating CL, if not addressed properly, could be complicated by the development of strains of parasites resistant to treatment in a fashion similar to what happened to plasmodium parasites when malaria was not appropriately treated. Under treatment, overdosing and uncontrolled use of drugs spread drug resistant of infectious organisms such as leishmania.[33-34]

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