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Sodium stibogluconate and paromomycin for treating visceral leishmaniasis under routine conditions in eastern Sudan

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Abstract

OBJECTIVES Among patients with primary and relapse visceral leishmaniasis (VL) in eastern Sudan, we determined the proportion eligible for treatment with sodium stibogluconate and paromomycin (SSG/PM) and, of these, their demographic and clinical characteristics; initial treatment outcomes including adverse side effects requiring treatment discontinuation; treatment outcomes by 6 months; and risk factors associated with initial (slow responders) and late treatment failure (relapses and post-kala-azar dermal leishmaniasis, PKDL).

METHODS A retrospective cohort study in Tabarak Allah Hospital, Gedaref Province, eastern Sudan, from July 2011 to January 2014.

RESULTS Of 1252 individuals diagnosed with VL (1151 primary and 101 relapses), 65% were eligible for SSG/PM including 83% children, almost half of them malnourished and anaemic. About 4% of individuals discontinued treatment due to side effects; 0.7% died during treatment. Initial cure was achieved in 93% of 774 primary cases and 77% of 35 relapse cases ($P < 0.001$). Among the 809 patients eligible for SSG/PM, 218 (27%) were lost to follow-up. Outcomes by six months among the 591 patients with available follow-up data were: definitive cure ($n = 506$; 86%), relapse ($n = 38$; 6%), treatment discontinuation ($n = 33$; 6%), PKDL ($n = 7$; 1%) and death ($n = 7$; 1%). Among those completing a full course of SSG/PM, relapses and under-fives were at significantly higher risk of early and late treatment failure, respectively.

CONCLUSION Whether SSG/PM as a first-line regimen is an undeniable progress compared to SSG monotherapy, it excluded a considerable proportion of VL patients due to drug safety concerns. We call for accelerated development of new drugs and treatment regimens to improve VL treatment in Sudan.

keywords Operational Research, sodium stibogluconate, paromomycin, Sudan, leishmaniasis, kala-azar

Introduction

Visceral leishmaniasis (VL) also known as 'kala-azar' is a life-threatening parasitic disease caused by the *Leishmania donovani* complex [1, 2]. It is the second largest global parasitic killer after malaria and schistosomiasis, responsible for about 50 000 deaths each year. More than 90% of all VL cases occur in India, Bangladesh, Nepal, Brazil and Sudan [3]. The disease is transmitted by the insect vector, the female phlebotomus sandfly, predominantly found in warm tropical regions. The disease involves the spread of the *Leishmania* parasite to different organs, such as the spleen, bone marrow and liver and generally presents with persistent fever, enlarged spleen and blood abnormalities, such as pancytopenia. Symptomatic VL is almost always fatal without treatment.

An ideal treatment for VL should be efficacious, well tolerated and easy to administer and should prevent subsequent relapses. It should also prevent post-kala-azar dermal leishmaniasis (PKDL) – a sometimes disseminated

and disfiguring skin rash after treatment of VL in Sudan. For several decades, VL treatment in Africa has been dependent on a 30-day regimen of intramuscular injections of sodium stibogluconate (SSG) [1]. Although this drug is effective, it is known to be toxic and requires long hospital stays (30 days) and its use in monotherapy may ultimately lead to drug resistance as observed in Asia [4]. The injections are also very painful, and this is of particular concern for children and may influence adherence.

A multicountry randomised controlled clinical trial conducted in four East African countries that compared SSG monotherapy for 30 days with sodium stibogluconate and paromomycin (SSG/PM) combination therapy for 17 days showed similar efficacy [5]. Based on these findings, WHO in 2010 recommended a combination of SSG/PM as first-line treatment in this region [6]. This regimen has the advantage of reducing in-hospital therapy time from 30 to 17 days [5], which is particularly useful at times of epidemics.

In Sudan, based on national and MSF protocol, SSG/PM is also recommended for patients who, prior to 2010, had received SSG monotherapy and then presented with a relapse, that is were considered a treatment failure. Although the rationale for this recommendation is not clear, it may have been related to lower cost and scarcity of evidence to recommend alternative drugs such as liposomal amphotericin B (AmBisome, Gilead Sciences, USA) [7]. There is, however, a genuine concern that the SSG/PM regimen may not be effective in patients who have previously received SSG as they may already be non-responsive to this drug and as such, effectively on 'monotherapy' with PM.

Médecins Sans Frontières (MSF), Switzerland, started a vertical programme in January 2010 for diagnosis and treatment of VL in Gedaref state of eastern Sudan – one of the most endemic regions in the world. Since July 2011, patients have been treated according to the above-mentioned recommendations. Only one study from South Sudan compared effectiveness of SSG/PM to SSG alone in routine setting [8]. In this large cohort, 17-day SSG/PM was associated with better survival and initial cure rates than 30-day SSG. However, this study only included primary VL cases, reported on patients who completed a full course of treatment, and assessed in-hospital mortality [8]. The proportion of VL patients who were actually treated with SSG/PM and the rate of treatment discontinuation were not reported.

To date, there are no reports on the effectiveness of SSG/PM used as a first-line regimen for both new and previously treated patients, under routine programme conditions. In order to obtain data on effectiveness and safety of SSG-PM in East Africa, MSF, DNDi and partners have conducted a pharmacovigilance study in four Eastern Africa countries where > 3,000 patients were treated, including 594 patients from Tabarak Allah site in Sudan. Such information would also be useful to assess the need for alternative therapies in Sudan. There are standardised ways of classifying types of VL and assessing their outcomes, including treatment failures (Box 1). Using this framework, we evaluated the first-line use of SSG/PM in new and previously treated patients in an MSF programme setting in eastern Sudan. Specific objectives were to determine the number (and proportion) eligible for SSG/PM treatment and of these (i) their demographic and clinical characteristics, (ii) initial treatment outcomes including the number with adverse side effects and those unable to complete a full course of treatment, (iii) follow-up treatment outcomes by 6 months, and (iv) risk factors associated with initial and late treatment failure.

Methods

This was a retrospective cohort study using routinely collected programme data, at Tabarak Allah Hospital in Gedaref state, eastern Sudan. This region is poor and remote with limited access to health care. It has the highest VL burden in Sudan. This hospital is one of the main VL treatment centres in the area, with an estimated target population of 754 638. Care is also provided for seasonal workers from Ethiopia and Eritrea. The project caters for diagnosis and treatment of VL and its associated medical conditions. All services provided by MSF are free of charge. The study included all patients diagnosed with primary and relapse VL between July 2011 and January 2014.

Management of visceral leishmaniasis

Diagnosis. Diagnosis of VL is performed in line with standardised MSF and MOH guidelines [9]. Individuals meeting the clinical case definition of VL (history of fever for 2 weeks or more with splenomegaly and/or lymphadenopathy and/or wasting) undergo further diagnostic evaluation. If there is no history of previous VL treatment, diagnosis is performed serologically either by positive rK39 rapid diagnostic test (DiaMed-IT-Leish, DiaMed AG) [10] or by a high titre (≥1:6400) of a direct agglutination test (DAT) [11]. The DAT is used in case of a negative rK39 test. Patients with borderline DAT titre (1:800–1:3200) undergo parasitological confirmation of VL by a lymph node aspiration (LNA). Patients with suspected VL but with a negative rK39 test and a low

DAT titre (<1:400) are evaluated for alternative illnesses and retested for VL if their illness persists.

Clinically suspected patients presenting with previous VL treatment are assessed by LNA and diagnosed as relapses if parasites are seen. LNA is graded using a logarithmic grading from 0 (0 parasites/1000 fields) to 6 (>100 parasites/field). If LNA is negative the test will be repeated after one to seven days. No spleen or bone marrow aspirates are performed in the centre.

Severity of VL is assessed clinically by the attending physician and is based on known factors associated with increased risk of death, including general weakness, old age, low body mass index and haemoglobin level [12].

First-line treatment consists of 17 daily intramuscular injections of SSG/PM combination (20 mg/kg generic SSG, Albert David, Calcutta, India and PM [Gland Pharma, India] at a dose of 15 mg/kg). Prior to July 2011, the regimen was SSG monotherapy administered as 30 daily injections at 20 mg/kg body weight. With the new regimen (SSG/PM), patients showing only partial clinical or parasitological response receive extended SSG monotherapy up to a maximum of 60 doses of treatment with a weekly test of cure (TOC) assessment. For individuals discontinuing PM due to intolerance (e.g. hearing loss as assessed by the whispering test and tuning fork), SSG is continued in monotherapy for a total of 30 days. VL patients are not eligible for SSG/PM if they present with HIV co-infection, pregnancy, other contraindication (s) to antimonials (e.g. renal failure), age ≤2 or ≥45 years, severe VL (i.e. having any severity factor) [12], non-response to SSG/PM (Box 1), or VL relapse after SSG/PM or liposomal amphotericin B. These individuals are offered second-line treatment consisting 10 consecutive days of 3mg/kg intravenous liposomal amphotericin B (AmBisome, Gilead Sciences).

Box 1 Definition of case classification and treatment outcomes for visceral leishmaniasis (VL), in eastern Sudan (2011–2014)

	Definition
Primary VL	Patient presenting with VL symptoms with no history of previous VL and currently diagnosed with VL. Diagnosis relies on a positive serological test for VL (rK39 based rapid test and/or DAT direct agglutination test) and/or a positive parasitological test (microscopic detection of *Leishmania* parasites in lymph node (LN) aspirate
Relapse	Patient with a history of previous VL and who then presents with symptoms of VL and a positive parasitological test
Initial cure	Patient who shows improvement of signs and symptoms at the end of treatment (fever resolution, haemoglobin increase, weight gain and spleen size regression) and a negative test of cure (TOC) if performed
Initial failure	A positive TOC (parasitological failure) and persisting clinical signs/symptoms. There are two types: slow responders and non-responders
Slow responder	Partial clinical response but TOC positive (PVL and VL relapse), or no improvement in clinical symptoms and signs with a decrease in parasite load at the end of treatment (for VL relapse).
Non-responder	Patients with no improvement in clinical symptoms and signs: (i) a positive lymph node aspirate after completion of treatment (for PVL), (ii) no decrease in parasite load at the end of treatment (for VL relapse)
Test of Cure (TOC)	Lymph node aspiration performed at the end of treatment to assess the parasitological response to therapy. A TOC is conducted for all VL relapse cases and for primary VL cases if indicated
Discontinuation due to toxicity	Discontinuation of treatment due to SSG/PM-related drug toxicity
Defaulter	A patient who took less than 14 doses of SSG/PM due to the patient leaving the hospital
Death	Death from any reason during treatment or up to 1 month of discharge
Definitive Cure	Patient with initial cure showing no signs and symptoms of the disease during follow-up. Typically definitive cure is ascertained at 6 months after treatment, although late relapse (after >6 months) is possible
Late treatment failure	Any patient after an initial cure who develops relapse or PKDL

Adapted from Salih *et al.* [7].

Patients are hospitalised during the entire course of treatment. At the end of treatment, initial cure is established clinically and parasitologically. Favourable clinical response comprises resolution involving four clinical features – clearance of fever, spleen regression, increased haemoglobin and/or weight gain. These patients do not undergo a TOC at discharge. A parasitological TOC by LNA is performed on day 17 in the case of poor or slow clinical response at the completion of treatment and in patients treated for VL relapse. Patients are considered to have initial treatment failure if they show parasitological failure (a positive TOC, i.e. detection of parasites in the LNA) at the end of 17 days of treatment.

At discharge, patients who receive a 6-month follow-up appointment are counselled to present at the health centre in case of recurrent symptoms of VL at any time. Before the scheduled 6-month follow-up appointment, health educators contact the patient by phone to remind him/her of the upcoming appointment. Not all patients are contactable, and among those who are contacted, not all are able to attend their appointment. Patients who miss their 6-month appointment are contacted and encouraged to return to the clinic for a follow-up assessment. If relapse is clinically suspected during the follow-up period, parasitological confirmation is performed. Patients with initial cure showing no clinical features of the disease at the 6-month scheduled follow-up visit are considered 'definitive cure' (Box 1).

Data collection and statistical analysis

The study was conducted between March and December 2014 and involved data of cases recorded between July 2011 and January 2014. Data were sourced from the kala-azar electronic database containing socio-demographic, clinical and laboratory data and collected using a standardised data collection tool; the database was updated daily by trained staff overseen by a supervisor. Information related to the study objectives was sourced from this database and validated using patient files.

Differences between groups were compared using the chi-square test. Measures of risk were assessed using relative risk (RR) and adjusted RRs using a step-wise backward log binomial regression model. Risk factors were independently assessed for 'initial treatment failure' and 'late treatment failure occurring any time after treatment completion'. Finally, 95% confidence intervals were used throughout and the level of significance was set at $P < 0.05$. Data were analysed using STATA 11 software (STATA Corporation, College Station, TX, USA).

Ethics approval

Ethics approval was received from the National Research Review Committee of Sudan and satisfied the Médecins Sans Frontières (Geneva, Switzerland) Ethics Criteria for studies using routinely collected data. The study also received approval from the Ethics Advisory Group of the International Union Against Tuberculosis and Lung Disease, Paris, France. As the study involved a retrospective analysis of routine programme data, informed patient consent was not applicable.

Results

Eligibility for SSG/PM treatment

There were 1252 individuals diagnosed with VL including 1151 (92%) primary and 101 (8%) relapse cases. Of these, 809 (65%) were eligible for SSG/PM and were started on this treatment. The reasons for non-eligibility are shown in Figure 1.

Demographic and clinical characteristics of patients starting SSG/PM

The demographic and clinical characteristics of the 809 patients started on SSG/PM are shown in Table 1. The cohort was predominantly male (66%) with a high proportion of children (47%) under 10 years. Almost half of all patients were acutely malnourished and had anaemia, and nearly seven in ten had an enlarged spleen.

Initial treatment outcomes and adverse side effects leading to treatment discontinuation

Initial treatment outcomes for the 809 individuals who started SSG/PM treatment are shown in Table 2. About 5% discontinued treatment due to death ($n = 6$) or side effects ($n = 33$). The most common reasons for stopping treatment were hearing problems, jaundice and severe anaemia (Figure 1). Initial cure was achieved in 93% of 774 primary cases and 77% of 35 relapse cases. About 19% were slow responders: 2% among primary cases and 17% among relapse cases, and almost all (23 of 24; 96%) were children.

Overall follow-up treatment outcomes by 6 months

Overall follow-up treatment outcomes by 6 months included 506 (63%) patients with definitive cure, 218 (27%) lost to follow-up, 38 (5%) relapses, 33 (4%) treat-

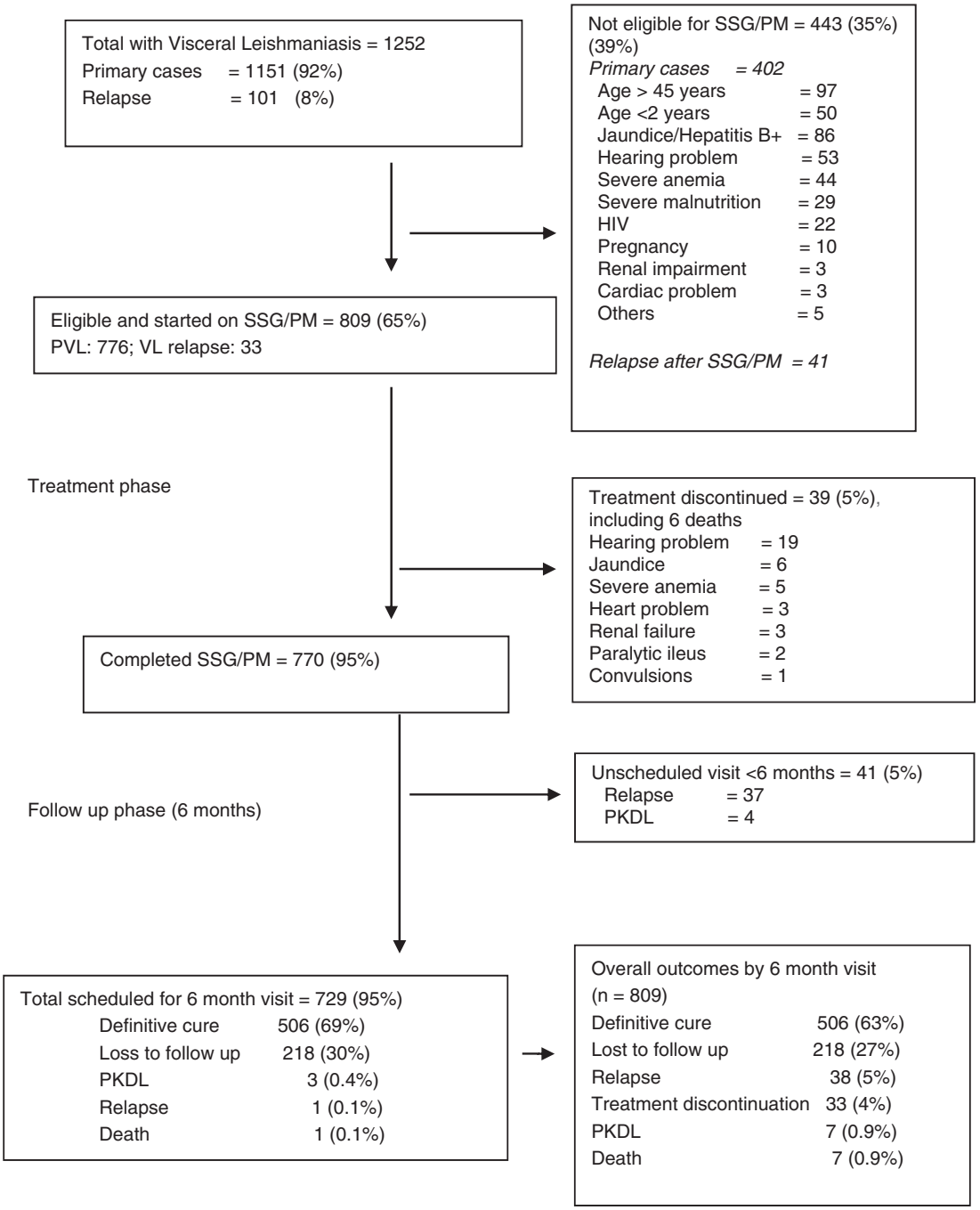

Figure 1 Flow chart showing the initial and late outcomes of patients diagnosed with primary and relapse visceral leishmaniasis and initiated on sodium stibogluconate/paromomycin treatment in eastern Sudan (2011–2014). SSG/PM, sodium stibogluconate and paromomycin; PKDL, post-kala-azar dermal leishmaniasis; HIV, human immunodeficiency virus.

ment discontinuation due to drug-related side effects, 7 (0.9%) PKDL and 7 (0.9%) deaths (Table 3). Among the 591 patients with available follow-up data, definitive cure was 85% with relapses and treatment discontinuation rates of 6%. Of note, 97% of the relapse cases presented before their scheduled 6-month follow-up visit [median

Table 1 Baseline demographic and clinical characteristics of patients with visceral leishmaniasis initiated on sodium stibogluconate/paromomycin in eastern Sudan (2011–2014)

Variable	*n* (%)
Total	809 (100)
Sex	
Female	276 (34)
Male	533 (66)
Age (years)	
<5	95 (12)
5–9	289 (36)
10–17	287 (35)
18+	138 (17)
Tribe	
Masalit	276 (34)
Falata-hosa-zabarma	174 (22)
Non-Arab tribes from Darfour	90 (11)
Tama	89 (11)
Non-Arab tribes from Chad	77 (10)
Arab tribes from Darfour	59 (7)
Arnga-Gemer	44 (5)
Category of visceral leishmaniasis	
Primary	774 (96)
Relapse	35 (4)
Nutritional status†	
Normal	390 (48)
Moderate malnutrition	341 (42)
Severe malnutrition	78 (10)
HIV status	
Positive	2
Negative	786 (97)
Unknown (Refused test)	28 (3)
Co-morbidities	
Lower respiratory tract infection	
Yes	41 (5)
No	768 (95)
Malaria	
Yes	47 (6)
No	762 (94)
Haemoglobin level (g/dl)	
Normal (>9 g/dl)	433 (54)
Mild/moderate anaemia (5–9 g/dl)	369 (46)
Severe anaemia (<5 g/dl)	7
Spleen enlargement on admission	
Yes	588 (73)
No	221 (27)

MUAC, mid-upper arm circumference; SAM, severe acute malnutrition; MAM, moderate acute malnutrition; W/H score, weight-for-height score; BMI, body mass index.
†Assessed as follows: age 6 months to 5 years by MUAC (SAM = <115 mm, MAM = 115–<125 mm); age 6 months to 9 years by MUAC (SAM = W/H score < −3, MAM = W/H score < −3); age 10–17 years by MUAC (SAM = W/H score <70%, MAM = W/H score 70 to <80%); and age >18 years by BMI (SAM = <16, MAM = 16 to <17).

Table 2 Initial treatment outcomes of sodium stibogluconate/paromomycin treatment among primary and relapse cases with visceral leishmaniasis in eastern Sudan (2011–2014)

	Total	Primary cases *n* (%)	Relapse cases *n* (%)	*P*-value*
	809	774	35	–
Initial outcomes				
Initial cure	746	719 (93)	27 (77)	<0.001
Slow responder	24	18 (2)	6 (17)	<0.001
Stopped treatment	33	31 (4)	2 (6)	
Died	6	6 (1)	–	–
Non-responder	–	–	–	–

**P*-values derived from chi-square test.

Table 3 Treatment outcomes by 6 months for patients with visceral leishmaniasis placed on sodium stibogluconate/paromomycin, stratified by VL history, eastern Sudan (2011–2014); *N* = 809

Treatment outcomes by 6 months	Total *n* (%)	Primary VL *n* (%)	VL relapse *n* (%)	*P*-value*
Definitive cure	506 (63)	483 (62)	23 (66)	0.69
Lost to follow-up	218 (27)	211 (27)	7 (20)	0.34
Treatment discontinued due to toxicity	33 (4)	31 (4)	2 (6)	0.65
Relapse	38 (5)	36 (5)	2 (6)	0.68
PKDL	7 (0.9)	6 (0.8)	1 (3)	0.27
Died	7 (0.9)	7 (0.9)	0 (0)	–
Total	809 (100)	774 (100)	35 (100)	–

VL, visceral leishmaniasis; PKDL, post-kala-azar dermal leishmaniasis.
**P*-values derived from chi-square test or Fisher's exact test.

time of presentation from initial cure = 2.2 months (IQR 1.7–3.8)], and the same was true for four (57%) of the PKDL cases [median time of presentation from initial cure = 4.1 months (IQR 3.0–5.0)].

Fourteen individuals declared as 'definitive cure' at 6 months returned with a relapse ($n = 5$) or with PKDL ($n = 9$) (median time of return after the scheduled 6-month visit = 4.1 months IQR 2.4–9.1). Similarly, five individuals who were declared lost at the 6-month follow-up visit returned with a relapse. The median time of presentation for these patients after the scheduled 6-month visit was 8.4 months (IQR 7.6–12.1 months). Thus, among 770 individuals who completed SSG/PM treatment, 6% were cases of relapse and 2% were cases of PKDLs.

Risk factors associated with initial and late treatment failure

Tables 4 and 5 show risk factors associated with initial and late SSG/PM treatment failure, respectively. Patients with a previous history of VL treatment (relapses) at initial presentation had a nine times higher risk of initial treatment failure than primary cases, and patients with malaria were at a 4.7 times higher risk. Being younger than 5 years was associated with a higher risk of late treatment failure.

Table 4 Risk factors associated with 'initial treatment failure' after a full course of sodium stibogluconate/paromomycin among primary and relapse visceral leishmaniasis patients in eastern Sudan, 2011–2014

Variable	*N*	Initial treatment failure *n* (%)	RR (95% CI)	Adjusted RR† (95% CI)	*P*-value
Total	770	24 (3)	–	–	–
Sex					
Female	257	10 (4)	1.4 (0.6–3.2)		
Male	513	14 (3)	1		
Age (years)					
<5	92	4 (4)	1.5 (0.5–4.9)		
5–9	283	11 (4)	1.3 (0.5–3.3)		
10–17	276	8 (3)	1		
18+	119	1 (1)	0.3 (0.04–2.3)		
Tribe					
Masalit	262	10 (4)	2.1 (0.6–2.6)		
Falata-hosa-zabarma	166	3 (2)	1		
Tama	85	1 (1)	0.7 (0.07–6.2)		
Arnga-Gemer	41	0 (0)	–		
Arab tribes from Darfur	55	4 (7)	4.0 (0.9–17.4)		
Non-Arab tribes from Darfur	86	3 (3)	1.9 (1.4–9.4)		
Non-Arab tribes from Chad	75	3 (4)	2.2 (0.5–10.7)		
Category of visceral leishmaniasis					
Primary	737	18 (2)	1		
Relapse	33	6 (18)	7.4 (3.2–17.5)	9.0 (3.7–22.0)	<0.001
Nutritional status‡					
Normal	378	9 (2)	1		
Moderate malnutrition	323	13 (4)	1.7 (0.7–3.9)		
Severe malnutrition	69	2 (3)	1.2 (0.3–5.5)		
Presence of malaria					
Yes	42	4 (10)	3.5 (1.2–9.7)	4.7 (1.6–13.7)	0.004
No	728	20 (3)	1		
Lower respiratory tract infection					
Yes	38	2 (5)	1.8 (0.4–7.2)		
No	732	22 (3)	1		
Haemoglobin level (g/dl)					
Normal (>9 g/dl)	416	12 (3)	1		
Mild/moderate anaemia (5–9 g/dl)	348	12 (3)	1.2 (0.5–2.6)		
Severe anaemia (<5 g/dl)	6	0	–		
Spleen enlargement on admission					
Yes	559	17 (3)	0.9 (0.4–2.2)		
No	211	7 (3)	1		

VL, visceral leishmaniasis; RR, risk ratio; CI; confidence interval, MUAC; mid-upper arm circumference; SAM, severe acute malnutrition; MAM, moderate acute malnutrition; W/H score, weight-for-height score; BMI, body mass index.
†Adjusted RRs only presented for those variables included in the multivariate model.
‡Assessed as follows: age 6 months to 5 years by MUAC (SAM = <115 mm, MAM = 115 to <125 mm); age 6 months to 9 years by weight-for-height score (SAM = W/H < −3, MAM = W/H score < −3); age 10–17 years by W/H (SAM = W/H score < 70%, MAM = W/H score 70 to <80%); age >18 years by BMI (SAM = <16, MAM = 16 to <17 kg/m^2).

Table 5 Risk factors associated with 'late treatment failure' among patients with visceral leishmaniasis treated with a full course of sodium stibogluconate/paromomycin in eastern Sudan, 2011–2014

Variable	*N*	Late treatment failure *n* (%)	RR (95% CI)	Adjusted RR† (95% CI)	*P*-value
Total	770	64			
Sex					
Female	257	23 (9)	1.1 (0.7–1.8)		
Male	513	41 (8)	1		
Age (years)					
<5	92	15 (16)	3.9 (1.5–10.3)	3.9 (1.5–10.3)	0.006
5–9	283	26 (9)	2.2 (0.9–5.6)	2.2 (0.9–5.6)	0.10
10–17	276	18 (7)	1.6 (0.6–4.1)	1.6 (0.6–4.1)	0.60
18+	119	5 (4)	1	1	
Tribe					
Masalit	262	23 (9)	1.2 (0.6–2.4)		
Falata-hosa-zabarma	166	12 (7)	1		
Tama	85	5 (6)	0.8 (0.3–2.2)		
Arnga-Gemer	41	3 (7)	1.0 (0.3–3.4)		
Arab tribes from Darfur	55	3 (5)	0.8 (0.2–2.6)		
Non-Arab tribes from Darfur	86	13 (15)	2.1 (1.0–4.4)		
Non-Arab tribes from Chad	75	5 (7)	0.9 (0.3–2.5)		
Category of visceral leishmaniasis					
Primary	737	61 (8)	1		
Relapse	33	3 (9)	1.1 (0.4–3.3)		
Nutritional status‡					
Normal	378	40 (11)	1		
Moderate malnutrition	323	19 (6)	0.6 (0.3–0.9)		
Severe malnutrition	69	5 (7)	0.7 (0.3–1.7)		
Presence of malaria					
Yes	42	3 (7)	0.9 (0.3–2.6)		
No	728	61 (8)	1		
Lower respiratory tract infection					
Yes	38	5 (13)	1.6 (0.7–3.8)		
No	732	59 (8)	1		
Haemoglobin level (g/dl)					
Normal (>9 g/dl)	416	31 (7)	1		
Mild/moderate anaemia (5–9 g/dl)	348	32 (9)	1.2 (0.8–2.0)		
Severe anaemia (<5 g/dl)	6	1 (17)	2.2 (0.4–13.8)		
Test of cure (TOC) on discharge					
Yes	138	9 (7)	1		
No	632	55 (9)	1.3 (0.7–2.6)		
Spleen enlargement on discharge					
Yes	17	3 (18)	2.2 (0.8–6.3)		
No	753	61 (8)	1		

VL, visceral leishmaniasis; RR, risk ratio; CI; confidence interval; MUAC; mid-upper arm circumference; SAM, severe acute malnutrition; MAM, moderate acute malnutrition; W/H score, weight-for-height score; BMI, body mass index.
†Adjusted RRs only presented for those variables included in the multivariate model.
‡Assessed as follows: age 6 months to 5 years by MUAC (SAM = <115 mm, MAM = 115 to <125 mm); age 6 months to 9 years by MUAC (SAM = W/H score < −3, MAM = W/H score < −3); age 10–17 years by MUAC (SAM = W/H score <70%, MAM = W/H score 70 to <80%); age >18 years by BMI (SAM = <16, MAM = 16 to <17).

Discussion

This is the first study assessing the effectiveness of the SSG/PM treatment regimen and safety under routine conditions for both primary and relapse VL. It reveals some important shortcomings. About 40% of patients were not treatment eligible due to various contraindications to SSG or PM. This figure may be lower in other treatment centres as some contra-indications considered in the MSF programme are relative (age <2 years), the clinical

hearing tests used to assess hearing loss lack specificity and alternative treatment (liposomal amphotericin B) was easily accessible (unlike the majority of treatment centres in Sudan). Mortality was low during SSG–PM treatment (<1%), but it must be emphasised that VL patients at increased risk of death (e.g. severe VL, patients >45 years) were treated with liposomal amphotericin B. Severe side effects resulting in treatment discontinuation occurred in 4%. Treatment outcomes by 6 months and after included a substantial but acceptable proportion of relapses (6%). Relapse cases and children under 5 years had a significantly higher risk of early and late treatment failure, respectively.

Importantly, relapse cases previously treated with SSG monotherapy who were then given combination treatment with SSG/PM had significantly lower initial cure rate and a higher proportion of slow responders. These negative outcomes signify poor therapeutic efficacy. As a test of cure was systematically done at the end of treatment in patients with relapse VL, unlike primary VL, this may have magnified the difference in treatment efficacy between the 2 groups. Nevertheless, there were also considerable numbers of relapses after an 'initial cure', which further begs the question of this treatment regime's effectiveness in patients previously treated with SSG.

Children constituted the great majority (83%) of patients on SSG/PM, with almost half under 10 years of age. Indeed, this predominance of paediatric VL cases is common to endemic areas such as in eastern Sudan [13]. As treatment has to be administered by (at least) two separate and painful daily intramuscular injections for a minimum of 17 days, this is clearly not an optimal treatment regime for this cohort. The finding that more than half of all patients also had moderate to severe malnutrition with associated tissue loss compounds this practical problem, because of difficulty in finding suitable injection sites. Almost all initial treatment failures were children who had to also endure painful weekly lymph node aspiration tests until reaching an initial cure. Thus, both diagnostics and drug administration subject children to painful procedures that might negatively influence treatment acceptability at the family level. This might partly explain the losses to follow-up observed post-treatment. Child-specific counselling and support services do not exist, but may have value to positively influence acceptability and outcomes.

The loss-to-follow-up, a matter of concern, is a general problem with VL treatment programmes and has been reported in several other studies [5, 8, 14]. The loss-to-follow-up seen in this programme is actually one of the lowest reported to date. The system of phoning patients both before their 6-month scheduled appointment reminding them to attend and afterwards if they missed it may have contributed to this relatively favourable picture. The reasons for loss-to-follow-up need to be investigated through qualitative research methods.

Strengths of this study are that it was conducted under routine programme conditions and thus reflects reality. This reality may however be different in centres that are not supported by MSF and that patients not eligible for SSG-PM and those who discontinued treatment due to drug side effects were reported upon [12]. Data were collected from a dedicated VL database regularly updated and supervised. The study was conducted in an MSF setting with staff well experienced in VL management.

Limitations are that patients lost to follow-up may include treatment failures and unascertained deaths, and we may thus have overestimated the effectiveness of SSG/PM. Specific studies on the reasons behind these losses would be useful. Those discharged without – or with a negative – TOC may still have had undetected parasites; as sensitivity of this test is low [6, 15], it may have led to overestimation of the initial cure rate.

There are a number of other operational issues that deserve further discussion. First, the fact that about 40% of patients were not eligible for SSG/PM shows that this treatment, although much better than the former SSG 30-day monotherapy, remains suboptimal. In a VL-endemic area like Sudan, one would expect that any first-line drug regimen could be administered for a larger majority of patients. More drug developments and clinical trials are needed to find a better first-line treatment than SSG/PM in East Africa, as it was achieved in South Asia with single-dose AmBisome [16]. Unfortunately, single or low cumulative doses of liposomal amphotericin B are not effective in East Africa [17]. In addition, access to AmBisome on a country-wide level in Sudan is hampered by international sanctions on Sudan (OFAC, U.S. Department of Treasury, 2011).

Second, a limited proportion of patients manifested side effects during treatment raising the concern on drug safety in poor settings, even when used by very experienced staff working within a well-resourced organisation such as MSF.

Third, the fact that several relapse and PKDL cases presented before and after the scheduled 6-month visit calls into question what the most appropriate follow-up schedule ought to be. In non-research settings, proper information given to patients at time of hospital discharge with an emphasis on consulting in case of recurring symptoms might be more cost-effective and practical than a fixed 6-month follow-up schedule.

Fourth, the standardised definitions for VL management warrant revision in Sudan. For example, terms such as 'initial' and 'definitive cure' have limitations when there is no diagnostic test that can ascertain parasite clearance ('cure'). Similarly, TOC is a test of 'cure' based on lymph node aspirates which, at best, has around 60% sensitivity [18]. From a patient perspective, the term 'defaulter' is judgmental, putting blame on patients, while the core problems of VL treatment lie within the health system [19]. A revision in this direction may be inspired by the recent guidance document on monitoring treatment outcomes for Asian countries by WHO/TDR [18].

Finally, patients who received SSG/PM combination therapy and returned with severe or chronic PKDL were offered a repeat course of SSG monotherapy as part of standard protocol. Of public health importance is that PKDL may serve as a reservoir for parasites that can be then transmitted by the sandfly [15]. Re-prescription of a drug that did not fully work in the first place cannot be justified from a public health or moral standpoint, without an evidence-based rationale. Continued use of such protocols may enhance resistance development and contribute to further endemicity of VL in eastern Sudan. Although published data on AmBisome treatment for Sudanese PKDL are scarce, it appears as a promising alternative while waiting for better (oral) treatment options [20].

In conclusion, this first study assessing the effectiveness of SSG/PM for both primary and relapse cases under routine conditions in Sudan highlights the urgent need for a better first-line treatment for VL in East Africa. Considering the remoteness of VL-endemic areas and the recurrent – and often massive – epidemics observed in East Africa, a short oral course of treatment – a track currently followed by the Drugs for Neglected Diseases Initiative – would be the preferred option.

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