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Ethiopian visceral leishmaniasis: generic and proprietary sodium stibogluconate are equivalent; HIV co-infected patients have a poor outcome

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Abstract

We evaluated generic sodium stibogluconate (SSG) (International Dispensary Association, Amsterdam) versus Pentostam® (sodium stibogluconate, GlaxoWellcome, London) under field conditions in Ethiopian patients with visceral leishmaniasis (VL; kala-azar). The 199 patients were randomly assigned to Pentostam ($n = 104$) or SSG ($n = 95$) in 1998/99; both drugs were given at 20 mg/kg intra-muscularly for 30 days. A clinical cure after 30-days treatment was achieved in 70·2% (Pentostam) and 81·1% (SSG). There were no significant differences between the 2 drugs for the following parameters: frequency of intercurrent events (vomiting, diarrhoea, bleeding or pneumonia) or main outcome (death during treatment and death after 6-month follow-up; relapse or post kala-azar dermal leishmaniasis at 6-months follow-up). Twenty-seven patients had confirmed co-infection with HIV. On admission, HIV co-infected VL patients were clinically indistinguishable from HIV-negative VL patients. The HIV co-infected VL patients had a higher mortality during treatment (33·3% vs 3·6%). At 6-month follow-up, HIV-positive patients had a higher relapse rate (16·7% vs 1·2%), a higher death rate during the follow-up period (14·3% vs 2·4%), and more frequent moderate or severe post kala-azar dermal leishmaniasis (27·3% vs 13·3%). Only 43·5% of the HIV-positive patients were considered cured at 6-months follow-up vs 92·1% of the HIV-negative patients. HIV-positive patients relapsing with VL could become a reservoir of antimonial-resistant *Leishmania donovani*.

Keywords: visceral leishmaniasis, chemotherapy, sodium stibogluconate, Pentostam, concurrent infections, HIV infections, efficacy, Ethiopia

Introduction

The endemic area of visceral leishmaniasis (VL; kala-azar) in north-east Sudan extends into the lowlands of western Ethiopia along the plain of the Atbara river and the tributaries of the Blue Nile, including the Rahad river. The parasite species is *Leishmania donovani* and its vector is *Phlebotomus orientalis*. Whereas in north-east Sudan patients are villagers with a male-to-female ratio of 1·5 : 1, and a median age of 9 years (VEEKEN *et al.*, 2000), in the Ethiopian focus many of the patients are young adult men migrated from other regions. Most of these migrant labourers have had no previous exposure to *Leishmania*, and are at risk of HIV infection. Médecins Sans Frontières-Holland (MSF) has supported the Ethiopian Ministry of Health in the treatment of VL patients since December 1997; over 1300 VL patients were treated during the first 3 years of support. The high cost (~US$200 per patient) of branded sodium stibogluconate (SSG; Pentostam®, GlaxoWellcome) led MSF to implement a series of 3 randomized field studies to establish whether treatment with generic SSG [Albert David Ltd, Calcutta, supplied by the International Dispensary Association (IDA), Amsterdam] is satisfactory. This product costs about 1/14th the price of Pentostam (i.e., ~US$13 per patient).The studies from Kenya (MOORE *et al.*, 2001) and north-east Sudan (VEEKEN *et al.*, 2000) have been completed; here we report the results of the study in Ethiopia, in an area with high prevalence of HIV co-infection.

Methods

The study was implemented from November 1998 to April 1999, in co-operation with the Tigray Regional Health Bureau. The study was planned for in Humera, a regional referral hospital. However, owing to escalation of the war against Eritrea, Humera town was evacuated and the study was carried out in a temporary treatment centre in Densha, 150 km south of Humera.

Patients

Inclusion criteria. Patients were identified using a modified WHO clinical case definition (WHO, 1996; MSF, 1999) of fever for >2 weeks, with exclusion of malaria, in combination with either splenomegaly or wasting. In cases meeting the case definition, VL was confirmed by a high titre *Leishmania* Direct Agglutination Test (DAT; titre $\geq 1 : 6400$). In cases with a borderline ($1 : 800 – 1 : 6400$) or negative DAT ($<1 : 800$), splenic aspiration was performed. Slides of splenic aspirates were checked by an independent microscopist at a later date. Given the harsh field conditions with failures in the cold chain and DAT antigen supply, the clinicians sometimes treated patients on clinical grounds, without parasitological or DAT confirmation.

Exclusions. Patients previously treated for VL were excluded. Informed verbal consent was given by the patient or his/her guardian/parent. Participation in the study, including HIV testing, was voluntary and patients would receive treatment with Pentostam if they were to decline. The study protocol was ethically reviewed by MSF and approved by the Tigray regional health authorities.

Sample size. A sample size of 91 patients in each arm was used, with a 90% power to detect at a significance level of $P = 0·05$ (2-tailed), a difference of 20% in cure, death, or relapse rate between the 2 groups.

Assignment

All consecutive patients who were newly diagnosed with VL from 12 November 1998 until 31 April 1999 were assigned to one of the 2 treatments, Pentostam or SSG, on the basis of the DAT test number. This number was recorded by a clerk in a single ledger prior to test results and prior to allocation. Patients with odd numbers received Pentostam, even numbers received SSG.

Masking

The study was not blinded—the volume and colour of the drugs are identical, but the multi-dose vials look different. The injection nurse knew which of the 2 drugs to give by colour coding of the patient treatment card. Nurses were trained and supervised in filling the registration forms.

Data collection

The following data were collected at admission or

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soon thereafter: name, age, gender, address, previous treatment, height, weight, spleen size (in cm from anterior axillary line to the furthest point of the spleen during quiet breathing), liver size (in cm in midclavicular line during quiet breathing), haemoglobin concentration, walking status (normal, with assistance, on stretcher), DAT result (number, titre, and date tested), parasitology result (tissue, grade, date). HIV status was tested with 2 rapid tests, Capillus (Trinity Biotech, Wicklow, Ireland) and HIV Spot (Genelabs Diagnostics, Geneva, Switzerland). HIV testing was not possible for all patients: some patients died before blood was drawn, and during one period of the study no test kits were available.

During treatment, intercurrent events, complications, and the causes of death were noted. At discharge the spleen size, liver size, haemoglobin concentration, weight, and presence of post kala-azar dermal leishmaniasis (PKDL) were noted.

Treatment

Treatment was given according to WHO and MSF schedules (WHO, 1996; MSF, 1999): 20 mg/kg daily for 30 days of either Pentostam or SSG intramuscularly. Both are colourless liquids, 1 mL contains 100 mg pentavalent antimony. The minimum dose was 2 mL (200 mg), no maximum upper limit was used. For injection volumes >10 mL the injection was given in 2 halves, in each buttock. All patients, whether in the study or not, received free treatment. Intercurrent illnesses were treated according to the MSF treatment protocols (MSF, 1999).

Outcome variables

The early outcomes were: initial cure (with or without parasitological confirmation), death during treatment and default during treatment. At follow-up at 6 months the outcomes were ultimate cure, relapse, and death since treatment. A patient was considered an initial cure if clinically well at discharge and having received ≥28 injections. In all patients who had splenomegaly at the end of treatment a test-of-cure (TOC) splenic aspirate was performed at day 25–30—if positive, the patient continued treatment until 2 consecutive TOCs performed weekly were negative. Owing to the migrant population and proximity to the front line, active follow-up was only partly possible. Patients were asked to return immediately if symptoms of VL recurred, and to return for follow-up after 6 months, even if well. At follow-up, an aspiration was performed only if relapse was suspected. When no relapse occurred by 6 months after discharge, the patient was considered an ultimate cure.

Statistical analysis

Data were entered in Excel (Microsoft) and analysed using Arcus Quickstat (*www.statsdirect.com*). For parametric data, the Z score test for comparison of means was used; for non-parametric data, the Mann–Whitney test was used. For categorical data the χ^2 test and Fisher's exact test were used.

Results

Patients

Between 1 November 1998 and 30 April 1999, 199 patients were enrolled. None of the patients declined to participate in the study, or refused HIV testing; 5 patients were treated outside the study, because of previous treatment. Of the 199 patients in the analysis, 194 patients had serological test results (DAT). Of these, 161 had a positive DAT result, 11 a negative, and 22 had a borderline DAT result. Fourteen patients had a splenic aspiration for confirmation of the diagnosis, and all 14 were positive: 3 with a positive DAT, 9 with a borderline DAT, and 2 with a negative DAT result. Thus 172 (86·4%) patients had serological and/or parasitological confirmation of VL, and 27 were treated on clinical grounds (WHO, 1996).

Allocation

Of the 199 patients, 104 were assigned to receive Pentostam and 95 to SSG. Six patients were wrongly allocated: 4 received Pentostam despite having an even DAT number, and 2 received SSG despite having an odd DAT number. Of the 27 patients treated on clinical grounds, 14 were assigned to Pentostam and 13 to SSG.

Clinical status

There were no significant differences in baseline characteristics [gender, age, duration of illness, ability to walk, weight, height, body mass index (BMI, calculated for patients aged ≥16 years), weight-for-height (calculated for patients <16 years), spleen size, and haemoglobin concentration] between the 2 treatment groups (Table 1).

HIV status

HIV Capillus and HIV Spot tests were performed on 146 and 149 patients, respectively, and 145 patients had results for both tests. Twenty-seven patients (18·6%) were found to be positive by both tests—18 in the Pentostam group and 9 in the SSG group ($P = 0·13$). In 6 patients HIV Spot and Capillus tests gave discordant results. In 112 patients (77%) both tests were negative; 49 patients were not HIV tested, as HIV test kits were not available in the field, and a further 5 patients had only a single test—all were negative. The 27 HIV-positive patients with VL were clinically indistinguishable from the 112 HIV-negative patients, with respect to baseline characteristics (Table 1) and common intercurrent events during treatment (Table 2). In addition (data available on request), there were no significant differences in the proportions with diarrhoea before treatment; vomiting or its duration or severity; bleeding or the sites of bleeding; malaria; pneumonia; tuberculosis whether diagnosed before or during treatment; peripheral neuropathy; zoster before or during treatment.

Outcome

In 86·4% of patients a laboratory-confirmed diagnosis (by DAT testing and/or microscopy) was made according to the routine MSF diagnostic algorithm in case of a high patient load during an epidemic. Twenty-seven patients (13·6%) were treated on clinical grounds, without laboratory confirmation. Of the patients treated on clinical grounds, 5 had no DAT performed, 13 had a borderline DAT, and 9 had a negative DAT. There was good evidence that most of the patients diagnosed clinically had VL: 26 had fever and splenomegaly and 1 had fever and hepatomegaly. Of the 27 patients treated on clinical grounds, 3 were HIV positive, 11 HIV negative and 12 untested. There was no difference in outcome between the 172 patients who had laboratory-confirmed VL and the 27 patients treated on clinical grounds. Of the 17 survivors in the latter group, in 6 the spleen became impalpable, and in 8 the spleen decreased in size; 3 developed PKDL after treatment.

Of 49 test of cure (TOC) splenic aspirates, only 1 was positive. In patients who did not have a TOC, cure was established as follows: the patient's fever had subsided, the spleen was smaller, and weight was being regained. At 6-months follow-up 70% of patients could be located and were clinically examined. This follow-up rate is successful considering that most patients are migrant labourers. For another 8·7% a history could be obtained from relatives or co-workers. Relapses (3), PKDL (15), and deaths (4) after discharge were few, and not significantly different between the 2 treatment groups.

Table 1. Comparison of the baseline characteristics of 199 Ethiopian patients with visceral leishmaniasis after randomization to receive either Pentostam or generic sodium stibogluconate (SSG)

	Pentostam ($n = 104$)		SSG ($n = 95$)		HIV positive ($n = 27$)		HIV negative ($n = 112$)	
Characteristic	Mean	Median	Mean	Median	Mean	Median	Mean	Median
Age (years)	26·1	24·5	30·0	25	29·9	28	24·3	23**
Sex (male/female)	92/12		88/7		25/2		101/11	
Duration of illness (months)	3·1	3	2·9	2	3·8	3	2·7	2***
Ability to walk (unaided/stick/stretcher)	40/43/21		32/41/22		11/9/7		47/49/16	
Weight (kg)	42·5	43·8	41·5	45·0	45·9	44·5	42·0	44·5
Height (cm)	160·4	165	158·0	165·5	167·2	166	158·8	164*
Haemoglobin (g/dL)	7·3	7·4	7·0	7	7·2	7·4	7·2	7·4
Body mass index (kg/m^2)	16·6	16·4	16·6	16·5	16·4	16·2	16·9	17
(adults)	($n = 86$)		($n = 79$)		($n = 27$)		($n = 92$)	
Weight-for-height (%)	79·8	83·5	81·1	82	N/A		80·7	83
(children)	($n = 16$)		($n = 15$)				($n = 23$)	
Spleen size (cm)	10·4	10	9·3	8	9·5	10	10·8	10
Mode of diagnosis								
Laboratory confirmed	90		82		23		101	
Clinical only	14		13		4		11	

Weight, and thus BMI and weight-for-height, are artificially high owing to 19 cases with ascites or oedema. All statistical comparisons between Pentostam and SSG are not significant. Between HIV-positive and HIV-negative patients, $P^*<0·05$; $^{**}<0·01$; $^{***}<0·001$.

Table 2. Intercurrent events among Ethiopian patients with VL during treatment with Pentostam or generic sodium stibogluconate (SSG)

	Pentostam	SSG	HIV positive	HIV negative
Diarrhoea	58/104 (55·8%)	55/95 (57·9%)	17/27 (63·0%)	62/112 (55·4%)
Vomiting	49/104 (47·1%)	37/95 (38·9%)	12/27 (44·4%)	40/112 (35·7%)
Pneumonia	23/104 (22·1%)	14/95 (14·7%)	3/27 (11·1%)	21/112 (18·8%)
Bleeding	58/104 (55·8%)	43/95 (45·3%)	18/27 (66·7%)	49/112 (43·8%)

No differences were statistically significant between Pentostam and SSG, nor between HIV-positive and HIV-negative patients.

The initial cure rate for the 2 treatment groups was 70·2% and 81·1%, respectively, for Pentostam and SSG ($P = 0·14$). The primary outcome parameters are shown in Table 3. There was no statistically significant difference between the 2 treatment groups in the increase of haemoglobin concentration (Pentostam 1·6 g/dL, SSG 2·1 g/dL; $P = 0·17$). However, there were significant differences in weight gain (Pentostam 0·1 kg, SSG 1·3 kg; $P = 0·03$), which was not confounded by ascites, and in decrease of spleen size after treatment (Pentostam 7·4 cm, SSG 5·9 cm; $P = 0·03$).

In total, 150 patients were considered cured after discharge; the remaining patients either died (48) or defaulted (1). Forty-nine patients were discharged with a negative TOC by splenic aspirate. Of the 101 patients who had no TOC after completing treatment, 98 had a

Table 3. Outcomes of 199 Ethiopian patients with visceral leishmaniasis, allocated at random in 1998/99 to treatment with Pentostam or generic sodium stibogluconate (SSG)

	Pentostam	SSG	HIV positive	HIV negative
Number treated	104	95	27	112
Died during treatment	30 (28·8%)	18 (18·9%)	9 (33·3%)	4 (3·6%)***
Defaulted	1	0	1	0
Completed treatment	73/104 (70·2%)	77/95 (81·1%)	17/27 (63·0%)	108/112 (96·4%)***
Positive/negative TOC	0/19 (0%)	1/29 (3·4%)	0/2 (0%)	0/36 (0%)
Followed up at 6 months	60/73 (82·2%)	58/77 (75·3%)	14/17 (82·4%)	85/108 (78·7%)
Clinically examined	52/60 (86·7%)	53/58 (91·4%)	11/14 (78·6%)	75/85 (88·2%)
History only	8/60 (13·3%)	5/58 (8·6%)	3/14 (21·4%)	10/85 (11·8%)
Died after discharge	4/60 (6·7%)	0 (0%)	2/14 (14·3%)	2/85 (2·4%)
Relapse	2/56 (3·6%)	1/58 (1·7%)	2/12 (16·7%)	1/83 (1·2%)*
PKDL Grade 2 or 3	9/52 (17·3%)	6/53 (11·3%)	3/11 (27·3%)	10/75 (13·3%)
Total deaths	34/90 (37·8%)	18/76 (23·7%)	11/23 (47·8%)	6/89 (6·7%)***
Final cure rate	56/90 (62·2%)	56/76 (73·7%)	10/23 (43·5%)	82/89 (92·1%)***

All statistical comparisons between Pentostam and SSG are not significant. Between HIV-positive and HIV-negative patients, $P^*<0·05$; $^{**}<0·01$; $^{***}<0·001$.

TOC, test-of-cure splenic aspirate; PKDL, post kala-azar dermal leishmaniasis.

spleen regression: to non-palpable (70), or just palpable but not measurable (28). One person did not show a regression of the enlarged spleen after treatment (DAT positive), and 2 patients did not have splenomegaly on admission (1 DAT positive, 1 DAT negative).

The overall mortality was 24·1%: 28·8% in the Pentostam group and 18·9% in the SSG group (not significant). The mean duration of treatment before death (Pentostam 11·1 days and SSG 10·1 days) did not differ significantly between the 2 groups. The main syndromes associated with death were: anaemia and bleeding (Pentostam 6, SSG 7), pneumonia (Pentostam 6, SSG 0), gastroenteritis (Pentostam 2, SSG 1). Other less-frequent associated symptoms were (16): shock, sepsis, jaundice, renal failure, vomiting, ascites, and peritonitis. In 8 deaths no cause was recorded.

The duration of illness before treatment was significantly longer in the patients who died (3·6 months) than in the survivors (2·8 months; $P = 0.028$). The frequency of intercurrent events (diarrhoea, vomiting, pneumonia, and bleeding) is shown in Table 2. Patients who had a positive HIV test both by Spot and Capillus had a significantly higher risk of dying during treatment as compared to patients who were negative by both tests. Mortality rate during treatment was 33·3% (HIV positive) and 3·6% (HIV negative) (relative risk = 9·25; $P = 0.00005$).

Follow-up

Overall, 78·7% of the surviving patients were passively followed-up: either clinically examined (70%), or reported by a family member or co-worker to be well (6·0%) or deceased (2·7%) (Table 3). At 6-month follow up there were 3 relapses (2 HIV positive, 1 HIV negative), 4 deaths (2 HIV positive, 2 HIV negative), and 15 cases of PKDL (3 HIV positive, 10 HIV negative, 2 untested). The final cure rate, using as a nominator the number of patients who were clinically cured at 6 months, and as a denominator the number of all those accounted for at 6 months (either cured, died, or relapsed), was 62·2% in the Pentostam group vs 73·7% in the SSG group ($P = 0.06$), and 92·1% in HIV-negative patients vs 43·5% in HIV-positive patients ($P = 0.000001$) (Table 3).

Discussion

A large proportion (90%) of our patients were male, and most were young adults. Our patients were severely ill, with only 36% being able to walk unaided and 22% being carried in on blankets by their companions. Their massively enlarged spleens, anaemia, and malnutrition on presentation, and the diarrhoea, bleeding, vomiting and pneumonia which frequently complicated their clinical course were entirely typical of the ~40 000 VL patients MSF has treated in the East Africa region since 1989. We found no clinically or statistically significant differences in outcome or side-effects between generic sodium stibogluconate (SSG) and Pentostam. We conclude that generic SSG (as manufactured by Albert David and quality tested by IDA) can be used safely and routinely for the treatment of VL patients. Continuous quality control of each batch produced must be done to guarantee safe treatment. The same conclusion was reached after similar studies among the Pokot tribe in Kenya, and in north Sudanese villagers. Taken together, the 3 studies represent the largest comparative field-based drug evaluation ever undertaken in VL. They have led to the adoption of inexpensive generic SSG in the region, not only by MSF but also by governments. It might be thought that a comparative study would be unnecessary, and that chemical analysis alone would suffice to show the drugs were equivalent. However, we met great resistance from many individuals and institutions to the introduction of a drug manufactured in India, and a project of this scale was required to overcome this prejudice. The mortality during treatment in Ethiopia (24·1%) was very high compared to previous cohorts we have treated (5·5%, SEAMAN *et al.*, 1993; 11%, SEAMAN *et al.*, 1996; 5·7%, VEEKEN *et al.*, 2000; 3·9%, MOORE *et al.*, 2001) and it rose to 31·7% by 6-months follow-up. This high value could be attributed to the 33·3% mortality during treatment among HIV-positive patients, rising to 47·8% by 6-months follow-up. Mortality in HIV-negative patients was only 3·6% during treatment, rising to 6·7% by 6 months.

We do not know the reason for the excess deaths among HIV co-infected Ethiopian VL patients. In a series of 51 treatment courses in Spanish HIV-positive VL patients, antimonials were frequently toxic, causing hyperamylasaemia (40%), acute pancreatitis (20%), renal failure (12%), and leucopenia (8%). Treatment had to be discontinued in 28%, and 12% of patients died (DELGADO *et al.*, 1999). In a comparative study of pentavalent antimonial and amphotericin B treatment of 99 HIV-positive VL patients in Spain, over 50% had an adverse drug event, 11% had to suspend treatment, 10% died during treatment, and the median survival after the diagnosis of visceral leishmaniasis was only 56 weeks (LAGUNA *et al.*, 1999). It is still unclear to what extent HIV co-infected patients with *L. donovani* will resemble those seen in Europe with *L. infantum*. The current 27 co-infected patients represent the largest cohort of *L. donovani*–HIV infected patients reported from either Africa or India. All our HIV-positive patients had 'typical' VL, as do 85% of those in Europe (WHO, 1999). However, we might easily have missed atypical cases who did not fit the clinical case definition, or were seronegative for *Leishmania* by DAT—almost 50% of European co-infected cases are seronegative (WHO, 1999). The number of relapses (2 of 12) and of PKDL (3 of 11) among HIV-positive patients were high. It is known that HIV co-infected patients frequently relapse and, when they do, they are often unresponsive to antimonials. In Europe, such patients are highly infectious to sandflies, particularly if their CD4+ cell count is low (MOLINA *et al.*, 1999). *Leishmania* parasites from relapsed patients can be shown *in vitro* to have become resistant to antimonials (FARAUT-GAMBARELLI *et al.*, 1997). This is of public health concern in Africa where *L. donovani* is spread from human-to-human by sandflies, and an animal reservoir is not known. Relapsed HIV co-infected patients may become an important reservoir of antimony-resistant *L. donovani*, either by being parasitaemic or by having PKDL. Although generic SSG is affordable and now available in Africa, there are no alternative antileishmanial agents suitable for field use at an affordable price; thus antimony-resistant VL would be effectively untreatable under the current circumstances.

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Announcements

African Index Medicus (AIM) Programme
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In order to give access to information published in or related to Africa and to encourage local publishing, the Association for Health Information and Libraries in Africa (AHILA), with the technical support of the World Health Organization, initiated a programme to create an international index to health literature generated in African countries: the *African Index Medicus*.

The creation of the regional index is a collaborative and participatory process. Firstly, African countries create national health databases using a common methodology. Local information services and products are provided for national health professionals. National production should ensure self-sufficiency and sustainability at country level and the tailoring of services according to local needs.

The various national databases are then merged into a regional database to which are added bibliographic records relating to health in Africa from other international existing sources such as WHO's WHOLIS, MEDLINE, POPLINE etc. to produce the *African Index Medicus* in printed or electronic form, eventually CD-ROM. It is distributed to African countries as part of an affiliated membership to AHILA for institutions outside the region.

At this stage, AHILA, with support from WHO, is looking for further sponsoring partners at bilateral level with African countries not yet participating in the Project. Sponsorship comprises equipment and training of staff and could be part of an information component of a health related project in the country, which may also include use of communications and CD-ROM.

Further information can be obtained from Mrs Lucilda Hunter, The Library and Documentation Centre, WHO Regional Office for Africa, P.O. Box BE 773, Belvedere, Harare, Zimbabwe.

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