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Treatment of Kala-Azar in Southern Sudan using a 17-Day Regimen of Sodium Stibogluconate Combined with Paromomycin: A Retrospective Comparison with 30-Day Sodium Stibogluconate Monotherapy

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Abstract. Médecins sans Frontières-Holland has treated > 67,000 patients with kala-azar (KA) in southern Sudan since 1989. In 2002, we replaced the standard regimen of 30 days of daily sodium stibogluconate (SSG) with a 17-day regimen of daily SSG combined with paromomycin (PM). We analyzed data for 4,263 primary KA patients treated between 2002 and 2005 in southern Sudan to determine the relative efficacy of the combination therapy regimen (PM/SSG). The initial cure rate among patients treated with PM/SSG was 97.0% compared with 92.4% among patients treated with SSG monotherapy. Relative efficacy of PM/SSG compared with SSG increased over the study period: odds of death in the PM/SSG group were 44% lower (odds ratio [OR] = 0.56, 95% confidence interval [CI] = 0.37–0.84) in 2002, 78% lower (OR = 0.22, 95% CI = 0.10–0.50) in 2003, and 86% lower (OR = 0.14, 95% CI = 0.07–0.27) in 2004–2005. In remote field settings, 17 days of SSG combined with PM gives better survival and initial cure rates than 30 days of SSG monotherapy.

INTRODUCTION

Visceral leishmaniasis (kala-azar [KA]) manifests with irregular bouts of fever, substantial weight loss, hepatosplenomegaly, pancytopenia, and increased susceptibility to bacterial infection. Kala-azar in southern Sudan is nearly 100% fatal if untreated.[1]

Médecins sans Frontières-Holland (MSF) began providing treatment for patients with KA in Western Upper Nile region of southern Sudan in 1989 after an epidemic that began in 1984 and which is estimated to have caused 100,000 deaths in this region from 1984 to 1994.[2] MSF treated more than 75,000 KA patients in southern and northern Sudan and Ethiopia between 1989 and 2005. Of 33,791 patients from southern Sudan, 22,809 were from the Western Upper Nile region and 10,982 were from the Eastern Upper Nile province.

A limited choice of drugs has been available for the treatment of KA. These drugs include sodium stibogluconate (SSG), meglumine antimonate, amphotericin B, and its lipid formulation AmBisome® (Gilead Pharmaceuticals, Foster City, CA), and pentamidine.[3] Two other drugs, miltefosine and paromomycin (PM) sulfate (formerly known as aminosidine), were licensed in India for KA treatment in 2002 and 2006, respectively. Three drugs (SSG, PM, and AmBisome®) have been used by MSF for treatment of KA in southern Sudan.[4]

We previously established in a randomized controlled trial that a combination of SSG plus PM was effective compared with SSG.[5] Since 1991, we used this PM/SSG combination for patients in southern Sudan who relapsed after conventional SSG treatment. This experience reassured us that PM/SSG was well-tolerated and effective, as was demonstrated in other studies.[6–10] In 2002, after a sharp increase in KA cases in the Eastern Upper Nile region, we began to use PM/SSG as first-line therapy for KA. Our immediate aim was to shorten the hospital stay of patients and thereby reduce overcrowding in MSF treatment centers. A manageable case load also reduces the risk of nosocomial outbreaks of infectious diseases associated with overcrowding of immunocompromised patients. We had found that outbreaks of dysentery were associated with high mortality rates during the 1989 epidemic in Western Upper Nile region.[11]

Paromomycin is a broad-spectrum aminoglycoside antibiotic that is effective against a wide range of bacteria and protozoa (including *Entamboeba* and *Giardia* spp.). We hypothesized that these properties of PM, its synergy with SSG, and the shorter duration of hospital stay associated with use of this drug would reduce the incidence of intercurrent infections and complications, and thereby reduce mortality rates. We therefore wished to evaluate the mortality rate of KA patients treated with PM/SSG combination therapy compared with patients who had received SSG monotherapy, after adjusting for confounding factors.

Organizing a comparative clinical trial was not possible under the prevailing wartime conditions in this extremely isolated and remote area. Therefore, we used the electronic archive of treatment data maintained by MSF since the early 1990s to analyze a large and recent data set (2002–2005) that bridged the period when PM/SSG was introduced. Our aim was to establish the efficacy of PM/SSG therapy under field conditions, to compare outcomes to those in patients treated with SSG monotherapy, and to use this evidence as the basis for clinical guidelines for MSF and other agencies operating in southern Sudan.

METHODS

Diagnosis, treatment, and discharge procedures. The diagnostic, treatment, and discharge procedures used were consistent with World Health Organization (WHO) guidelines.[12] Briefly, patients with KA who had no previous history of treatment were termed patients with primary KA and patients with KA who reported a history of any previous treatment of KA were termed patients with relapsed KA.

We diagnosed KA in clinically suspected patients by a high titer (≥ 1:6,400) in a direct agglutination test (DAT; freeze-dried *Leishmania* antigen was provided by the Royal Tropical

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Institute, Amsterdam, The Netherlands), by microscopy of splenic or lymph node aspirates, or on rare occasions when laboratories were not functioning, by clinical judgment and the patient's response to treatment.

Standard treatment of primary KA comprised daily intramuscular injections of SSG (manufactured by Albert David Ltd., Calcutta, India and supplied by the International Dispensary Association, Amsterdam, The Netherlands) at a dose of 20 mg/kg (minimum dose = 200 mg; no maximum dose) for 30 days.

The PM/SSG combination therapy regimen comprised 17 daily intramuscular injections of generic SSG at a dose of 20 mg/kg and daily intramuscular injections of paromomycin sulfate (manufactured by Pharmamed Parenterals Ltd., Malta supplied by the International Dispensary Association, Amsterdam, The Netherlands) at a dose of 15 mg/kg (equivalent to 11 mg/kg of PM base). PM/SSG was withheld during 2002 and 2003 from all female patients of child-bearing age. Since 2004, combination therapy has been withheld only from pregnant women. PM/SSG was administered only at MSF treatment centers which had a permanent expatriate doctor, and these centers also had access to parenteral antibiotics and therapeutic feeding.

In cases of primary KA treated with SSG, a test-of-cure (TOC) was performed on spleen or lymph node aspirates if the patient did not respond clinically to treatment. If the TOC result was positive, daily SSG injections were continued until the results of two consecutive weekly TOCs were negative. Patients whose results remained positive for parasites after 60 SSG injections received SSG plus PM or AmBisome®. In cases of primary KA treated with PM/SSG, if the TOC result was positive at day 17, then additional SSG monotherapy was given. Severely ill KA patients were treated with AmBisome® until 2005 when we introduced a formal risk assessment using a scoring system. Thereafter, patients at high risk of death were treated in special care areas with hydration, therapeutic nutrition, antibiotics, and AmBisome®, and then treated with PM/SSG when their condition improved. We termed this "combined AmBisome®-paromomycin-stibogluconate treatment" (CAPST).

On discharge, patients were given an identification card to be presented on re-admission to a treatment center for post kala-azar dermal leishmaniasis (PKDL) or relapse. Patients with relapsed KA always received a diagnosis based on the results of an aspirate because a positive DAT result does not distinguish between patients who are cured and those who have experienced relapse. These patients were treated with 17 daily injections (dose = 15 mg/kg) of PM plus 30–60 daily injections of SSG (dose = 20 mg/kg). Patients who experienced two or more relapses were treated with six intravenous doses of 4–6 mg/kg of AmBisome® on alternate days. Patients with severe PKDL were treated with SSG, or if not responding, a combination of PM/SSG, until their condition improved.

Data. Data for this study were obtained from an electronic archive of KA patient records from MSF treatment centers in southern Sudan. Patient records were stored electronically since the early 1990s. From 2002 through 2005, MSF treatment centers in the Eastern Upper Nile region were located in Abuong, Wudier, Lankien, Magang, Pieri, Bimbim, Atar, and Rupbuot, and in the Western Upper Nile region in Nimne.

Data entry. Patient demographic, diagnosis, treatment, and discharge data were handwritten on a card during a patient's stay at a treatment center. MSF staff in Lokichoggio entered data from these cards into EpiInfo version 6 (Centers for Disease Control and Prevention, Atlanta, GA). Because of time and resource constraints, all data were single-entered.

Data cleaning. If possible, anomalous, inconsistent, or missing values were identified and corrected. If not possible, these values were recoded as missing. Particular attention was given to the drug regimen, which was cross-referenced with monthly summary statistics for each treatment center. Body mass index (BMI) values were re-calculated, and child weight-for-height Z-scores were generated using WHO Anthro 2005 software (Department of Nutrition, WHO, Geneva, Switzerland).

Inclusion criteria. This study included only primary KA patients admitted during 2002–2005 who received either 30 days of SSG monotherapy or 17 days of PM/SSG combination therapy. Duration of therapy was calculated as the interval between admission and discharge and may not have reflected the exact number of doses given. Because of irregularities in drug administration (no treatment on Sundays) and delay between admission and start of treatment and/or between end of treatment and discharge, we used a stay of up to 40 days for monotherapy and up to 20 days for combination therapy. Patients who defaulted (self-discharge against medical advice) were excluded.

Outcomes. Our primary outcome was being discharged alive after treatment. Death during treatment is a marker of lack of efficacy or toxicity of treatment. Our secondary outcomes were occurrence of diarrhea, vomiting, and bleeding during treatment, and weight gain and remission of splenomegaly at time of discharge.

Variables. The following patient data were used in our study: age, sex, self-reported duration of illness prior to admission, calculated weight-for-height Z-score (for patients $\leq$ 5 years of age), reported weight-for-height percentage (for patients between 5 and 15 years of age, re-calculated BMI (for patients $\geq$ 15 years of age), spleen size on admission and discharge (Hackett grade), hemoglobin level (g/dL), walking status for patients $\geq$ 5 years of age (walking normally, walking with assistance, or carried on a stretcher), occurrence of diarrhea (yes or no), bleeding (yes or no), and vomiting (yes or no) during treatment. Malnourishment was defined as a Z-score < -3 for patients $\leq$ 5 years of age or a weight-for-height score $< 75\%$ for patients 5–15 years of age or a BMI $<$ 14 kg/m^2 for adults. Weight gain was expressed as the percentage weight on admission.

Statistical analysis. Characteristics of patients and outcomes were compared by chi-square test and *t*-test. Confounders were identified by their association with treatment group and outcome. Crude odds ratios (ORs) were calculated for death comparing monotherapy with combination therapy, and ORs adjusted for confounders were estimated using multivariable logistic regression, with standard errors adjusted for clustering by treatment center. Effect modification was identified by chi-square test of the homogeneity of odds ratios across strata, and confirmed in multivariable models by likelihood ratio tests. All statistical analyses were performed using Stata Release 9 (Stata Corporation, College Station, TX).

RESULTS

The archive contained the records of 6,432 patients treated by MSF in southern Sudan from 2002 through 2005, of whom 5,689 (88.5%) were treated for primary KA, 388 (6.0%) for relapsed KA, and 355 (5.5%) for PKDL. The relatively small number of records (507) for patients treated in 2005 were combined with the 1,273 patients treated in 2004. Of the 5,689 primary KA cases, 1,268 (22.3%) were treated with SSG monotherapy, 4,242 (74.6%) were treated with PM/SSG combination therapy, and 179 (3.2%) were treated with Ambisome® either as monotherapy or in combination with SSG, PM, or both. Of the 1,268 SSG monotherapy patients, 2 had no recorded outcome, 74 (5.8%) were treated for > 39 days, and 14 (1.2%) of the remaining 1,192 defaulted. Of the 4,242 PM/SSG patients, 6 had no recorded outcome, 1,121 (26.4%) were treated for > 19 days, and 30 (1.0%) of the remaining 3,115 defaulted.

Characteristics of the remaining eligible patients on which our subsequent analyses were based are summarized in Table 1 for each drug regimen. Patient characteristics differed between the two treatment groups (age, sex, walking status, nutritional status, and spleen size on admission). These differences suggest that PM/SSG recipients were generally at higher risk of death than SSG recipients: the PM/SSG treatment group had higher proportions of children, malnourished patients, and stretcher cases, but less massive splenomegaly. Hemoglobin was measured only during 2003; during this year, patients on PM/SSG had lower mean hemoglobin levels. The PM/SSG treatment group contained a disproportionate number of male patients, particularly during 2002 and 2003.

The primary outcome (death) and two of the secondary outcomes (diarrhea and bleeding) were less common among the PM/SSG patients than the SSG patients (Table 2). Weight gain was higher among patients who received SSG monotherapy. Remission of splenomegaly was the similar in each

TABLE 1
Patient characteristics in each treatment group*

Characteristic	Year							
	2002		2003		2004–2005		Overall	
Treatment	SSG	PM/SSG	SSG	PM/SSG	SSG	PM/SSG	SSG	PM/SSG
No. of primary KA cases	589	613	233	1,504	356	968	1,178	3,085
Male (%)	29.0	65.9	14.4	57.3	51.6	52.1	32.9	57.4
P	< 0.001		< 0.001		0.78		< 0.001	
Age groups (%), years								
0–5	14.4	25.3	8.2	27.2	29.9	26.1	17.8	26.5
6–14	18.3	37.7	6.0	31.2	27.0	29.3	18.5	31.9
≥ 15	67.2	37.1	85.8	41.6	43.1	44.7	63.6	41.7
P†	< 0.001		< 0.001		0.02		< 0.001	
Walking status (age > 5 years)								
Unassisted	23.8	27.8	33.3	17.2	20.2	36.9	24.9	25.5
Assisted	66.2	63.1	60.4	66.2	62.3	48.1	64.0	59.9
Stretcher	10.0	9.2	6.3	16.6	17.5	15.0	11.1	14.6
P†	0.39		< 0.001		0.001		0.02	
Mean duration of illness (months)	1.72	1.62	1.96	1.42	1.78	1.63	1.79	1.53
P‡	0.16		< 0.001		0.06		< 0.001	
Duration of illness > 3 months (%)	5.4	4.4	9.6	3.3	10.0	5.7	7.6	4.3
P†	0.43		< 0.001		0.007		< 0.001	
Mean WFH (%)	74.09	77.54	78.67	74.40	75.10	75.85	74.79	75.30
P‡	0.04		0.09		0.44		0.49	
Mean BMI for age ≥ 15 years (kg/m^2)	15.11	15.28	15.69	15.38	15.33	15.72	15.31	15.48
P‡	0.32		0.06		0.05		0.07	
WFH Z-score < –3 for age ≤ 5 years (%)	36.5	38.3	31.6	45.7	34.0	34.5	34.8	40.9
P†	0.78		0.23		0.92		0.11	
WFH < 75% for > 5 years age < 15 years (%)	8.3	8.7	0.0	44.5	22.9	40.6	14.2	34.9
P†	0.91		0.001		0.002		< 0.001	
BMI < 14 kg/m^2 for age ≥ 15 years (%)	22.7	19.1	14.3	20.0	15.1	14.4	19.1	18.0
P†	0.29		0.07		0.82		0.55	
Malnourished as defined above (%)	22.2	20.1	15.0	34.6	22.8	27.4	21.0	29.4
P†	0.36		< 0.001		0.09		< 0.001	
Mean Hb (g/dL)	Not recorded		9.21	8.62	Not recorded		9.21	8.62
P‡	–		0.001		–		0.001	
Hb < 7.5 g/dL (%)	Not recorded		18.9	25.4	Not recorded		18.9	25.4
P†	–		0.11		–		0.11	
Spleen size (%)								
Not palpable	8.3	8.8	6.3	9.5	4.0	8.7	6.6	9.1
Hackett grade 1	21.0	25.9	32.3	30.1	25.4	31.2	24.5	29.6
Hackett grade 2	53.4	52.8	41.7	41.4	44.9	40.5	48.5	43.4
Hackett grade 3	14.9	10.8	14.4	16.5	22.3	16.5	17.0	15.4
Hackett grade 4 or 5	2.4	1.7	5.4	2.5	3.4	3.2	3.3	2.5
P†	0.11		0.07		0.003		< 0.001	
Clinical diagnosis (no DAT or aspirate)	9.7	2.6	9.0	2.1	23.0	44.4	13.6	15.5
P†	< 0.001		< 0.001		< 0.001		0.12	

* *P* value indicates evidence of difference in proportion or means comparing SSG and PM/SSG treatment groups. SSG = sodium stibogluconate; PM/SSG = paromomycin/sodium stibogluconate; KA = kala-azar; WFH = weight for height; BMI = body mass index; Hb = hemoglobin; DAT = direct agglutination test.
† By chi-square test.
‡ By *t*-test.

TABLE 2
Patient outcomes in each treatment group*

Outcome	Year							
	2002		2003		2004–2005		Overall	
Treatment	SSG	PM/SSG	SSG	PM/SSG	SSG	PM/SSG	SSG	PM/SSG
No. of primary KA cases	589	613	233	1,504	356	968	1,178	3,085
Death (%)	5.1	3.6	8.6	3.5	11.2	1.8	7.6	3.0
P†	0.20		< 0.001		< 0.001		< 0.001	
Vomiting (%)	32.2	30.9	29.6	32.2	22.5	18.1	28.8	27.5
P†	0.55		0.43		0.07		0.39	
Diarrhea (%)	34.5	23.2	36.5	26.1	46.6	28.5	38.5	26.3
P†	< 0.001		0.001		< 0.001		< 0.001	
Bleeding (%)	1.9	2.8	6.9	1.9	7.0	4.0	4.4	2.8
P†	0.30		< 0.001		0.02		0.006	
Mean weight gain (%)	5.85	3.33	2.08	3.22	5.44	3.51	5.1	3.3
P‡	0.002		0.24		0.007		< 0.001	
Spleen size on discharge (%)								
Not palpable	86.6	88.9	85.9	86.6	75.7	78.7	82.1	84.0
Hackett grade 1	5.5	6.0	10.1	8.4	16.9	13.6	10.9	10.0
Hackett grade ≥ 2	7.7	5.1	4.0	5.0	7.5	7.8	7.0	6.1
P†	0.41		0.79		0.42		0.52	

* Chi-square test P value indicates statistical significance of difference in proportions comparing SSG and PM/SSG treatment groups; t-test P value indicates statistical significance of difference in means comparing SSG and PM/SSG treatment groups. For definitions of abbreviations, see Table 1.
† By chi-square test.
‡ By t-test.

group. There was strong evidence of an increasing death rate by year of treatment among patients treated with SSG (P = 0.0005, by score test for trend of odds), and of a decreasing death rate among patients treated with PM/SSG (P = 0.02, by score test for trend of odds).

Crude and adjusted odds ratios for death are shown in Table 3. Confounding variables were age (death is more likely at young and old ages), walking status, duration of illness, and nutritional status. Sex was not associated with death, either within treatment groups or overall. The higher proportion of children in the PM/SSG group in 2002 and 2003 is reflected in the adjusted ORs for these two years. The increasing efficacy of PM/SSG compared with SSG over time does not permit us to estimate a summary OR for the period 2002–2005. There was no effect modification (interaction) by age or by any of the other variables. Table 3 also shows two multivariable models stratified by an age ≤ 5 years or an age > 5 years, which adjust for confounding by age-specific factors (e.g., walking status).

For patients ≤ 5 years of age, there was no interaction with year of treatment; thus, a summary OR is reported. This shows 64% lower odds of death (OR = 0.36, 95% CI = 0.23–0.57) among children treated with PM/SSG compared with SSG monotherapy after adjusting for age.

For patients > 5 years of age, the interaction with year of treatment remains, but the ORs for death comparing PM/SSG with SSG in 2003 and 2004–2005 are similar after adjustment for confounders. Patients treated with PM/SSG in these two years had 86–88% lower odds of death compared with patients who received SSG monotherapy (summary adjusted

TABLE 3
Odds ratios for death during treatment*

Characteristic	Year							
	2002		2003		2004–2005		Overall	
Treatment	SSG	PM/SSG	SSG	PM/SSG	SSG	PM/SSG	SSG	PM/SSG
All patients								
No.	589	610	233	1,504	355	967	1,178	3,081
Deaths	30	22	20	53	40	17	90	92
Adjusted odds ratio (95% CI)†	0.56 (0.37, 0.84)		0.22 (0.10, 0.50)		0.14 (0.07, 0.27)		LR test for interaction with year P = 0.004	
Age ≤ 5 years								
No.	85	154	19	409	106	252	210	815
Deaths	16	13	4	35	18	8	38	56
Adjusted odds ratio (95% CI)‡	0.36 (0.18, 0.72)		0.53 (0.16, 1.77)		0.18 (0.07, 0.44)		0.36 (0.23, 0.57)	
Age > 5 years								
No.	470	407	182	1006	222	650	875	2,066
Deaths	10	9	15	17	20	8	45	34
Adjusted odds ratio (95% CI)§	1.17 (0.89, 1.53)		0.14 (0.12, 0.16)		0.12 (0.04, 0.34)		LR test for interaction with year P = 0.002	

* LR test = likelihood ratio test; CI = confidence interval. For definitions of other abbreviations, see Table 1.
† Adjusted for age and malnutrition, and clustering by treatment center.
‡ Adjusted for age and clustering by treatment center.
§ Adjusted for age, malnutrition, walking status, length of illness prior to admission, and clustering by treatment center.

OR for patients treated during 2003 and 2004–2005 = 0.14, 95% CI = 0.08–0.26).

DISCUSSION

Our results provide strong evidence that a 17-day regimen of daily PM/SSG combination therapy was associated with reduced odds of death during treatment of primary KA when compared with a 30-day regimen of daily SSG monotherapy. Our study is not a randomized controlled drug trial, but a retrospective field evaluation conducted within the constraints of operating under wartime conditions in a sparsely populated area. The overall death rate in our study for patients treated with SSG (7.6%) is consistent with previous studies in southern Sudan, which reported death rates of 10.9% (observed over the period 1990–1991), 7% (in a 1993 trial), and 8.1% (observed over the period 1998–2002).[5,11,13] The overall death rate in our study for patients treated with PM/SSG (3%) compares favorably with these figures, and our findings confirm the results we found with PM/SSG combination therapy in an earlier (1993) randomized controlled trial in southern Sudan, and in a proof of concept study conducted in Kenya 20 years ago.[5,6]

The apparent increasing efficacy of PM/SSG compared with SSG, which is due to the diverging death rates in each treatment group, is a paradox. One likely explanation is that during the period 2002–2005, we adopted a hub-and-spoke system of treatment centers. PM/SSG was administered only at hub centers; these benefited from an expatriate doctor and access to parenteral antibiotics and therapeutic feeding; thus, our results would be biased in favor of PM/SSG. However, during 2002 and 2003, most patients in our study (86% and 87%, respectively) were treated at one hub site (Lankien) where both regimens were administered. During 2004–2005, when most patients were evenly distributed across four sites, three of these sites (accounting for 64% of patients) administered both drug regimens. Apart from exclusion of women, reasons behind differential assignment of patients to either SSG or PM/SSG within a treatment site could not be obtained retrospectively; thus, ascertainment of bias was not possible. Another explanation for the diverging death rates might be that because the most severely ill patients at some of the PM/SSG sites received Ambisome® or CAPST, this would remove the most severely ill patients from the PM/SSG treatment group.

Although we have attempted to control for differences between the two treatment groups (age, nutritional status, duration of illness), our results remain susceptible to confounding. Considering also the sources of bias mentioned above, the ORs for death should be interpreted with some caution. Despite these caveats, our study benefits from being based on a large number of unselected patients who were treated under field, as opposed to clinical trial conditions.

PM/SSG combination therapy was associated with a lower incidence of one or more episodes of diarrhea during treatment compared with SSG monotherapy. This result is consistent with the antimicrobial properties of PM. However, the observation period for PM/SSG patients is shorter than for SSG patients, and there was better availability of parenteral antibiotics in the larger treatment centers where PM/SSG was used. Similarly, one or more episodes of bleeding (mainly epistaxis) occurred in 2.8% of PM/SSG patients during treatment, which was lower than the overall rate of 4.4% seen among SSG patients in this study and the rate of 6.4% we published previously.[13] The reduction in bleeding could be caused by the antimicrobial effect of PM on nasal staphylococcal infection, to a more rapid improvement in platelet counts, or to less SSG-induced thrombocytopenia. Alternatively, it may also be attributable to a shorter period of observation and availability of parenteral antibiotics. Patients who received PM/SSG gained less weight, and this is probably related to a shorter duration of supplemental feeding that was provided for patients at all treatment centers. We could not establish the relative efficacy of PM/SSG compared with SSG in preventing relapse (thus, we report initial, not final, cure rates) and PKDL from our dataset.

Most PM/SSG patients (67%) were admitted for 18–19 days. Of the 1,121 PM/SSG patients excluded from the analyses because they received > 19 days treatment, 837 (75%) were discharged within the next four days, which suggested that our criteria did not exclude PM/SSG patients who had an unsatisfactory response to treatment. The excluded PM/SSG patients did not differ from the PM/SSG patients who received 18–19 days of treatment, and their inclusion in the analysis tended to improve the relative benefit of PM/SSG.

Combination therapy with PM/SSG has several important advantages. First, the shorter duration of treatment and hospitalization results in decongestion of the treatment centers, and reduces the risk of nosocomial disease outbreaks. Second, the costs of treatment are significantly less: the cost of drugs is similar for the SSG and PM/SSG regimens (US $16–17 for an average 35-kg patient), but the costs of hospitalization (food and accommodation) are reduced. Finally, we remain committed to the principle of using combination therapy for KA to prevent or delay the emergence of resistance to antileishmanial drugs. Incontrovertible evidence for the relative efficacy of PM/SSG compared with SSG can only be provided by further randomized controlled trials, which may not be feasible in southern Sudan for the foreseeable future. In the meantime, we consider that the evidence provided by our study supports our continued use of this regimen for primary KA in southern Sudan.

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REFERENCES

1. Zijlstra EE, el-Hassan AM, 2001. Leishmaniasis in Sudan. Visceral leishmaniasis. *Trans R Soc Trop Med Hyg 95 (Suppl 1):* S27–S58.
2. Seaman J, Mercer AJ, Sondorp E, 1996. The epidemic of visceral leishmaniasis in western Upper Nile, southern Sudan: course and impact from 1984 to 1994. *Int J Epidemiol 25:* 862–871.
3. Guerin PJ, Olliaro P, Sundar S, Boelaert M, Croft SL, Desjeux P, Wasunna MK, Bryceson AD, 2002. Visceral leishmaniasis: current status of control, diagnosis, and treatment, and a proposed research and development agenda. *Lancet Infect Dis 2:* 494–501.
4. Ritmeijer K, Davidson RN, 2003. Royal Society of Tropical Medicine and Hygiene joint meeting with Medecins sans Frontieres at Manson House, London, 20 March 2003: field research in humanitarian medical programmes. Medecins sans Frontieres interventions against kala-azar in the Sudan, 1989–2003. *Trans R Soc Trop Med Hyg 97:* 609–613.
5. Seaman J, Pryce D, Sondorp HE, Moody A, Bryceson AD, Davidson RN, 1993. Epidemic visceral leishmaniasis in Sudan: a randomized trial of aminosidine plus sodium stibogluconate versus sodium stibogluconate alone. *J Infect Dis 168:* 715–720.
6. Chunge CN, Owate J, Pamba HO, Donno L, 1990. Treatment of visceral leishmaniasis in Kenya by aminosidine alone or combined with sodium stibogluconate. *Trans R Soc Trop Med Hyg 84:* 221–225.
7. Scott JA, Davidson RN, Moody AH, Grant HR, Felmingham D, Scott GM, Olliaro P, Bryceson AD, 1992. Aminosidine (paromomycin) in the treatment of leishmaniasis imported into the United Kingdom. *Trans R Soc Trop Med Hyg 86:* 617–619.
8. Thakur CP, Olliaro P, Gothoskar S, Bhowmick S, Choudhury BK, Prasad S, Kumar M, Verma BB, 1992. Treatment of visceral leishmaniasis (kala-azar) with aminosidine (= paromomycin)-antimonial combinations, a pilot study in Bihar, India. *Trans R Soc Trop Med Hyg 86:* 615–616.
9. Thakur CP, Bhowmick S, Dolfi L, Olliaro P, 1995. Aminosidine plus sodium stibogluconate for the treatment of Indian kala-azar: a randomized dose-finding clinical trial. *Trans R Soc Trop Med Hyg 89:* 219–223.
10. Thakur CP, Kanyok TP, Pandey AK, Sinha GP, Zaniewski AE, Houlihan HH, Olliaro P, 2000. A prospective randomized, comparative, open-label trial of the safety and efficacy of paromomycin (aminosidine) plus sodium stibogluconate versus sodium stibogluconate alone for the treatment of visceral leishmaniasis. *Trans R Soc Trop Med Hyg 94:* 429–431.
11. Seaman J, Mercer AJ, Sondorp HE, Herwaldt BL, 1996. Epidemic visceral leishmaniasis in southern Sudan: treatment of severely debilitated patients under wartime conditions and with limited resources. *Ann Intern Med 124:* 664–672.
12. World Health Organization, 1996. *Manual on Visceral Leishmaniasis Control.* Geneva: World Health Organization.
13. Collin S, Davidson R, Ritmeijer K, Keus K, Melaku Y, Kipngetich S, Davies C, 2004. Conflict and kala-azar: determinants of adverse outcomes of kala-azar among patients in southern Sudan. *Clin Infect Dis 38:* 612–619.