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Letter to the Editor (New Data)

High mortality among older patients treated with pentavalent antimonials for visceral leishmaniasis in East Africa and rationale for switch to liposomal amphotericin B

Visceral leishmaniasis (VL; kala azar), a fatal disease if left untreated, is one of the most neglected tropical diseases. Poor and remote areas of South Asia and East Africa are the most affected.

Pentavalent antimonial (SbV) drugs have been the mainstay of VL therapy in East Africa for the past 70 years. These drugs are administered parenterally for 30 days. Their potential for toxicity is high among VL patients, and drug-induced renal failure, acute pancreatitis, or cardiotoxicity can result in death.

A growing body of clinical evidence shows that patients ≥45 years of age with leishmaniasis are at higher risk of death or severe adverse reactions during SbV treatment (1-6). Two separate studies conducted by Médecins Sans Frontières (MSF) in South Sudan showed that VL patients ≥45 years old treated with the SbV drug sodium stibogluconate (SSG) had 4.6 (odds ratio [OR]; 95% CI: 2.7-7.7) (1) and 6.8 (relative risk [RR]; 95% CI: 4.4-10.4) (6) times higher risks of dying compared with younger patients (Table).

More recent data analysis of MSF's VL programs in Uganda and Ethiopia showed similar findings. In Uganda, where patients were primarily treated with either SSG or another SbV drug, meglumine antimoniate, age ≥45 years was the strongest independent risk factor for

mortality with an adjusted OR of 38.2 (95% CI: 11.8-123.2) (4). In Ethiopia, patients ≥45 years old treated with SSG had 6.6 (OR; 95% CI: 3.2-13.9) higher risk of death compared to patients 5-29 years old (2).

These risk ratios translated into case fatality rates (CFR) of 12% (2) to 30%, with three of the four studies demonstrating CFR 26-30% (Table) (1, 4, 6).

This brief meta-analysis of MSF VL data shows that treatment with SbV of patients ≥45 years old results in unacceptably high mortality in East Africa. This may be caused by SbV toxicity, increased disease severity, or a combination of both. It is therefore urgent to evaluate potentially safer and more rapidly active treatments in this age group, such as liposomal amphotericin B (LAmB), miltefosine, or combination therapies (e.g. SbV with paromomycin for 17 days), and adapt national guidelines accordingly.

LAmB (total dose 30 mg/kg) is now used by MSF in East Africa as compassionate treatment for patients ≥45 years old, and for other groups of patients at increased risk of complications or death due to SbV (e.g. HIV-TB co-infected, severely sick, or pregnant patients). Of 87 patients ≥45 years old treated with LAmB by MSF in Sudan, Kenya, and Ethiopia since 2002, 7 patients have died, giving a CFR of 8% (unpublished data).

Despite recent drug price decreases, the cost of LAmB remains higher than SbV drugs, hindering its wider use. However, the incremental cost for increasing LAmB use would be expected to be relatively modest, since patients ≥45 years old represent a relatively small

fraction (1.7-6.4%) of VL patients (Table). With a relatively small investment in LAmB, mortality among VL patients ≥45 years old in East Africa could be reduced with little delay.

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Table. Summary of MSF studies examining age ≥45 years as a possible risk factor for death among VL patients treated with SbV in East Africa

Study	Country	Number of VL patients analyzed (≥45 years old)	Risk of death in patients ≥45 years old	CFR among patients ≥45 years old
Collin et al. 2004 (1)	South Sudan	3,200 (110)	OR = 4.6 [95% CI 2.7-7.7][a]	28.2%
Seaman et al. 1996 (6)	South Sudan	2,791 (179)	RR = 6.8 [95% CI: 4.4-10.4][b]	26.3%
Mueller et al. 2009 (4)	Uganda	1,801 (30)	OR = 38.2 [95% CI 11.8-123.2][c]	30.0%
Herrero et al. 2009 (2)	Ethiopia	2,177 (106)	OR = 6.6 [95% CI 3.2-13.9][d]	12.3%

a. Adjusted only for sex; comparator age group: 16-24 years

b. Multivariable analysis; comparator age group: 5-14 years

c. Multivariable analysis; comparator age group: 6-15 years

d. Multivariable analysis; comparator age group: 5-29 years

MSF, Médecins Sans Frontières; VL, visceral leishmaniasis; SbV, pentavalent antimonial; OR, odds ratio; RR, relative risk; CFR, case fatality rate