Safety and Effectiveness of Liposomal Amphotericin B (AmBisome®) treatment for Visceral Leishmaniasis (VL) under routine programme conditions in Vaishali, Bihar, India.

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Liposomal Amphotericin B (AmBisome®)

- Safest available drug for VL treatment.
- First-line treatment for VL in resource rich settings.
- Phase II studies showed:
  - High efficacy (89-100%).
  - Good safety profile
- No Phase III or IV study data available.
- High cost of the drug.

MSF-Spain VL project in Bihar

Project Timing & Location

- Project implementation started in Hajipur Sadar Hospital and the RMRIMS (Patna) in July 2007
- Decentralisation strategy / ambulatory treatment started at PHCs in 2008
  - PHC-Vaishali (Feb 08)
  - PHC-Goraul (April 08)
  - PHC-Mahua (June 08)
  - PHC-Raghapur (Dec 08)

Objectives

- To monitor tolerability and safety of first line AmBisome®, at a total dose of 20mg/kg body weight, under routine programme conditions.
- To monitor effectiveness of AmBisome®.

Methodology

- Prospectively monitored and evaluated a cohort of VL patients.
- AmBisome® at 5 mg/kg body weight on day 0, 1, 4 & 9 (WHO recommended, 2005)
- Inclusion:
  - Patients diagnosed with ***primary VL.***
  - Clinical case definition & rK39 dipsticks or spleen aspirate +.
- Exclusion:
  - Patients previously treated with full course of AmB and AmBisome®.
  - Patients with relapse, <2 years old, HIV or TB co-infected.
  - PKDL

Continued…

- Safety monitoring (all patients in 1st year):
  - Clinical assessment

- Effectiveness end points:
  - At the end of treatment (day 10): all patients in first year of programme
  - Final cure at 6 months (only first 250 patients)
    - Clinically well
    - If clinically suspected, parasitological clearance

1st year (16th July 2007 – 16th July 2008) Kala azar project MSF, Vaishali district, Bihar

	July-December 2007						Jan-June 2008						
VISCERAL LEISHMANIASIS **MSF-SPAIN IN BIHAR**	JUL. 07	AUG. 07	SEPT. 07	OCT. 07	NOV. 07	DEC. 07	JAN. 08	FEB. 08	MAR. 08	APR. 08	MAY O8	JUN. 08	**Total**
Screened	109	308	271	371	319	287	284	365	459	442	570	465	**4250**
Positive (Rk39)	65	155	128	149	149	174	176	232	247	211	273	229	**2188**
Total registered	53	147	118	137	137	166	160	201	242	193	254	205	**2013***

***VL patients treated with AmBisome® = 1924**

Characteristics on admission

Total (N)	= 1924
Age (years) Median (range)*	**16 (1 – 80)**
M: F ratio	**1.3 : 1 (1078/838)**
Spleen Size (cm)*	**4.5 (0 – 25)**
Hemoglobin (gm/dl)*	**7.8 (2 – 15.5)**
Severe malnourished**	**88 (4.57%)**
Moderate malnourished***	**346 (17.98%)**
Musahar cast N (%)	**169 (8.78%)**
Respiratory infections	**94 (4.9%)**
Gastro-intestinal	**64 (3.3%)**

*For age, spleen & HB: Median (range)
**Severe malnourished: BMI > 16kg/m^2 or W/H <70%
***Moderate malnourished: BMI 16- 18kg/m^2 or W/H 70-80%

Main Adverse Events

Grade	Adverse event	Number = 151 (7.8%)
Adverse events	**Nausea, vomiting, chills, rigor, fever**	**102 (5.3%)**
	Increased tendency to bleed	**7 (0.4%)**
	Increased back pain	**21 (1.1%)**
	Generalized itching and swelling	**18 (0.9%)**
Serious adverse events	**Progressive lip swelling (Hypersensitivity)**	**3 (0.2%)**

- **No clinical or laboratory findings of Cardiac, Hepatic, Nephro and Oto-toxicities.**

End-of-Treatment Effectiveness

- Initial cure rate at discharge= 98.7%
- Defaulter rate= 0.8%
- Death rate= 0.5%

Outcomes for 6m follow-up (n=250)

	At the end of treatment	At 3-month FU	At 6-month FU
Stopped treatment due to ADR	**3**	**-**	**-**
Defaulters	**2**	**-**	**-**
Loss to follow up	**0**	**22**	**41***
Died	**0**	**1**	**3***
No. of patients remain in the follow up	**245**	**222**	**201**
Cure rate, intent to treat (%)	**98%**	**89%**	**81%**
Cure rate, per protocol % (CI95)**	**98% (0.96-0.99%)**	**97% (0.94–0.99%)**	**96% (0.93-0.98%)**

*** Cumulative numbers**
**** Confidence interval at 95%**

Clinical Markers for Improvement

	At the end of Treatment	At 3-months FU	At 6-months FU
Hb gain (gm/dl) Median (range)	**0.7 (-2.7 to 3.8)**	**3.1 (-1 to 9.4)**	**3.3 (-1 to 4.2)**
Spleen size regression (cm)	**- 5 (-1 to -14)**	**0***	**0**
Weight gain (kg) ≤ 15 years	**0.64 (-3 to 7)**	**2 (-5 to 10)**	**2 (-3 to 7)**
BMI (kg/m^2) ≥16 years	**0.2 (-0.4 to 0.7)**	**1.6 (-0.5 to 3.2)**	**1.5 (-1.2 to 4.3)**
Severe malnourished	**20/23 (87%)**	**4/23 (17%)**	**2/23 (8.7%)**

***at 3-months follow up time, 15 patients presented with palpable spleen but clinically free from VL and 8/15 were splenic aspiration negative.**

Conclusions

- AmBisome® (20 mg/kg) shows high effectiveness (96%), under routine programme conditions.
- Extremely safe: only 0.08 adverse event per treatment (1 year data).
- High tolerability.

Key Issues & Recommendations

- Need for cold chain.
- High drug cost.
- New implementation programmes with AmBisome® (15 mg/kg) and closely monitored under field conditions should be undertaken.
- Further combination studies with AmBisome® as the main drug, to be combined with other drugs are a priority.

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