AmBisome:
The Experience in East Africa

LEAP
LEISHMANIASIS
EAST AFRICA PLATFORM

ASTMH meeting

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LEAP study group

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Outline of Presentation

1. Summary of important published data concerning efficacy of AmBisome against *L. donovani*: includes RCTs, field cohorts and case series

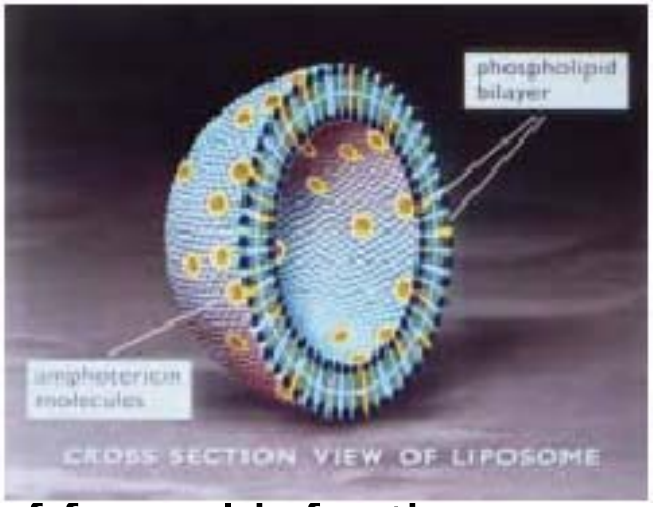
2. Experience of LEAP 0104 where AmBisome was used as a rescue treatment against VL

3. Collation of other unpublished data on the use of AmBisome in East Africa: field cohorts/small case series, where effectiveness has been evaluated by:
   - cure determined by parasitology at end of treatment
   - 6-month follow-up NOT routinely done
   - active reporting of all failures/deaths after end of treatment collected
   - initial cure rate, deaths and failures presented as n(%)

AmBisome for VL in East Africa

- Antimonials have been the main treatment in SSA
  = Toxicity, drug resistance, availability
- Current use is compassionate/ 2nd line
- Increased interest as a first line and as a candidate for combination treatments
- No clear-cut recommendations on doses of AmBisome in SSA
  = Effective doses undetermined, mostly 2nd line
- Not registered (on National Drug List of Sudan and Ethiopia, unregistered in Kenya and Uganda)

Product Overview



- Indications: prophylaxis & empiric Rx of fungal infections in immunocompromised, candidiasis & aspergillosis, cryptococcus (HIV)…& VL. Dose varies accordingly
- Chemistry: liposomal formulation of Ampho B (macrocyclic polyene antibiotic)
- Formulation: API is entrapped in a lipid bilayer of small unilamellar liposomes (cholesterol, HSPC, DSPG)
- Particulars: 50mg of API per vial, stored <25°C, photosensitive, shelf-life 36 months, reconstituted via filter for IV use with 12mL water and then dextrose solution (1:19), incompatible with saline, if opened use in 24h (2-4°C)
- Contraindications: known hypersensitivity to constituents

AmBisome in VL treatment (early studies: up to 2005)

Number of patients	Total and daily doses (mg/kg)	Efficacy (95% CI) [IC or DC]	References
N = 10 N = 10 N = 10	14mg (7 doses; days 1,2,3,4,5, 6,10) 10mg (5 doses; days 1,2,3,4 & 10) 6mg (3 doses; days 1, 5 & 10)	100% [NA] = IC/DC 100% [NA = IC/DC 100% [NA = IC/DC	Berman JD *et al.*, 1998 (India)
N = 10 N = 10 N = 10	14mg (7 doses; days 1,2,3,4,5,6, 10) 10mg (5 doses; days 1,2,3,4 & 10) 6mg (3 doses; days 1, 5 & 10)	100% [NA] = IC/DC 90% [NA = IC/DC 20% [NA = IC/DC	Berman JD *et al.*, 1998 (Kenya)
N = 17	15mg (single dose)	100% [NA] = IC/DC	Thakur CP *et al.*, 2001 (India)
N = 20 N = 20 N = 20	15mg (3mg/day, 5 doses) 10mg (2mg/day, 5 doses) 5mg (1mg/day, 5 doses)	100% [84 – 100] = IC 90% [68 – 99] = IC 84% [60 – 97] = IC	Sundar S *et al.*, 1997 (India)
N = 26 N = 24 N = 27	10mg (2 doses, days 1 & 2) 10mg (2 doses, days 1 & 5) 5mg (single dose)	92% [75 – 99] = IC 100% [88 – 100] = IC 89% [71 – 98] = IC	Sundar S *et al.*, 1998 (India)
N = 46 N = 45	5mg (single dose) 5mg (5 doses, daily)	91% [79 – 98] = DC 93% [82 – 99] = DC	Sundar S *et al.*, 2001 (India)
N = 28 N = 28 N = 28	15.0mg (3mg/day, 5 doses, daily) 7.5mg (1.5mg/day, 5 doses, daily) 3.75mg (0.75mg/day, 5 doses, daily)	96% [NA] = IC 97% [NA] = DC 96% [NA] = IC 93% [NA] = DC 96% [NA] = IC 89% [NA] = DC	Sundar S *et al.*, 2002 (India)
N = 203	7.5mg (single dose)	96% [92 – 98]= IC 90% [85 – 94]= DC	Sundar S *et al.*, 2003 (India)
N = 41 N = 30	20mg (10mg daily, 2 days) 20mg (4mg daily, 5 days)	97.6% [NA] = DC 90.0% [NA] = DC	Syriopoulou V *et al.*, 2003 (South Europe/Greece)

Efficacy of single doses of AmBisome in immuno-competent patients

Dose, n	IC/DC (%), [95% CI]	References
India, 5.0mg *(n=27)*	89% [71-98] = IC	Sundar S et al., 1998
India, 5.0mg *(n=46)*	91% [79-98] = DC	Sundar S et al., 1998
India, 7.5mg *(n=203)*	96% [92-98] = IC 90% [85-94] = DC	Sundar S et al., 2003
India, 10mg *(n=304)*	95% [93-98] = DC	Sundar S et al., 2010
India, 15mg *(n=17)*	100% = IC/DC	Thakur CP et al., 2001

Recent studies and case series

Examples	Doses	Number treated	Efficacy (ITT)
Routine Program, India (Sinha et al., 2010)	20mg MD	251	98.8% (DC)
Case series, Sudan (52 relapses, 12 complicated cases) (Muller et al., 2006)	15-49mg MD	64	54.7% (IC)
P2 RCT, India (Sundar et al., 2008)	LD+MLT	181	91–98% (DC)
DNDi, India (2010)	LD+MLT LD+PM	160 158	97.5% (DC)

Consensus on doses of AmBisome for immunocompetent patients (Bern et al., 2006)

Region	Doses (mg/kg)	Recommendations
ZVL (Med., Middle East, Brazil)	20	2 daily divided doses
AVL (South East Asia)	10-15	1-3 divided doses
Sub Sahara Africa	?	30mg/kg in multiple divided doses

Experience of 0104 study

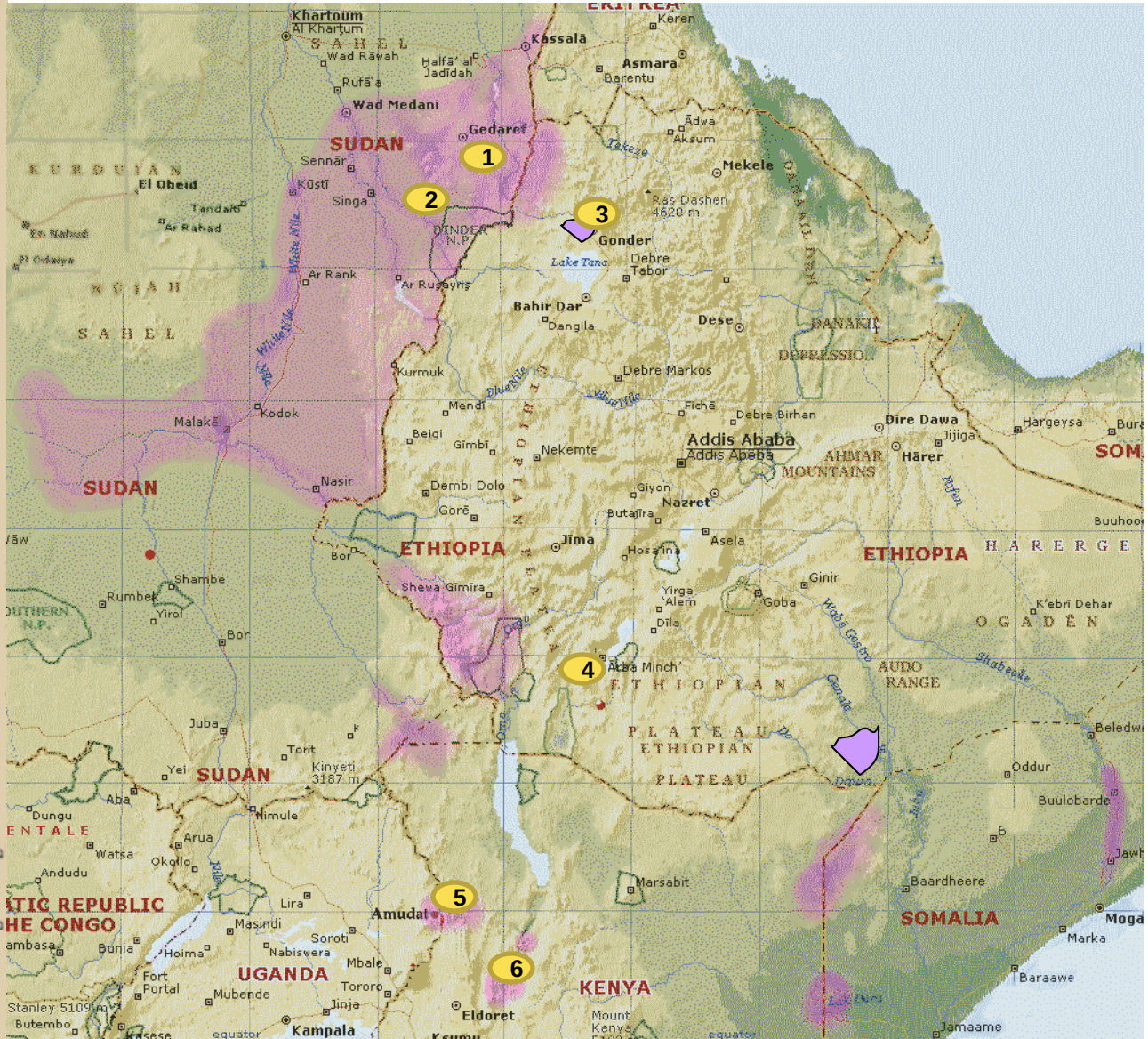
- Recent clinical trial comparing SSG v PM v SSG/PM completed in 2010
- AmBisome used as rescue treatment
- During the trial, rescue treatment regimen was standardized to 30mg/kg (3mg/kg given over 10 doses, day 1-10)
- All people given the rescue treatment had recent anti-leishmanial treatment
- Exclusion criteria of the original trial removed the most severely ill patients

Methods

- Rescue treatment was given to the following patients:
  - Patients withdrawn due to an AE to the original trial treatment (SSG, PM, Combination)
  - Initial failure: patients who remained parasite positive at end of treatment with clinical symptoms and signs of VL
  - Relapses: patients discharged after initial treatment and re-presenting with clinical symptoms and signs of VL and positive parasitology

- Initial cure was assessed after AmBisome 'rescue treatment' through repeat parasitology (spleen or bone marrow)
- After end of treatment, all relapses to rescue treatment that re-presented (passively) were recorded; patients were followed up for 6 months after *initial treatment* had been completed
- Routine follow-up for a further 6 months was not done/documented after rescue treatment
- Data are presented as initial cure (n(%), after rescue treatment), with n(%) of relapses re-presenting back

LEAP Participating Centres in 0104



1 Kassab Hospital, University of Khartoum, *Sudan*

2 Um el Kehr centre, MSF-Holland, *Sudan*

3 Gonder Hospital, Gonder University, *Ethiopia*

4 Arba Minch Hospital, Addis Ababa University, *Ethiopia*

5 Amudat Hospital, Makerere University, *Uganda*

6 Centre for Clinical Research, KEMRI, *Kenya*

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Baseline data of 0104 patients given AmBisome rescue treatment

Indicator		
Age (years)	Mean (SD)	17.8 (10.8)
	Median (IQR)	14 (9 to 25)
Sex, n (%)	Male	54 (61.4)
	Female	34 (38.6)
HIV status, n (%)	Positive	5 (5.7)
	Negative	76 (86.4)
	Not tested	7 (7.9)
Nutritional Status	Severely underweight	17 (19.3)
	Underweight	37 (42.1)
	Normal/overweight	34 (38.6)
Haemoglobin (g/dl)	Mean (SD)	7.6 (1.8)
	Median (IQR)	7.3 (6.2 to 8.9)
Spleen size (cm)	Mean (SD)	8.4 (4.7)
	Median (IQR)	8 (6 to 10.8)

N=88; SD= standard deviation; IQR=inter-quartile range

Treatment outcomes (I)

Trial arms /dose	Outcome of rescue Tx [ICR = Initial Cure Rate]	N (and %) Relapses
SSG: 20 mg/day (30 days) **(n=14)**	13/14 (92.9)	0 (0)
PM: 15mg/kg/day (21 days) **(n= 19)**	18/19 (94.7)	3 (16.7)
PM: 20mg/kg/day (21 days) **(n= 30)**	30/30 (100)	1 (3.3)
PM/SSG (17 days) PM: 15mg/kg/day SSG: 20mg/kg/day **(n= 25)**	25/25 (100)	3 (12.0)
Total (n = 88)	**86/88 (97.7)**	**7 (8.1)**

Treatment outcomes after rescue(II)

Trial sites	Total dose/kg (days)	Outcome of rescue Tx [ICR = Initial Cure Rate]	Relapses N (and %)
Ethiopia, Gondar (n=19)	30mg (10 days)	18/19 (94.7)	4 (22.2)†
Ethiopia, A/Minch (n=5)	30mg (10 days)	5/5 (100)	1 (20)π
Kenya, KEMRI (n=13)	14mg (7 days)	13/13 (100)	2 (15.4)
Kenya, KEMRI (n=1)	21mg (7 days)	1/1 (100)	0 (0)
Kenya, KEMRI (n=5)	30mg (10 days)	5/5 (100)	0 (0)
Sudan, Kassab (n=45)	30mg (10 days)	44/45 (97.8)	0 (0)
Total (n=88)	**-**	**86/88 (97.7)**	**7 (8.1)**

- 2 patients died during rescue, 7 patients subsequently relapsed
- 9/88 (10.2%) patients relapsed or died during or after rescue

Other Unpublished data

- Two cohorts were obtained from 2 trial sites where patients were treated with AmBisome outside of clinical trials
  - Kassab Hospital (Sudan)
  - Gondar Teaching Hospital (Ethiopia)
- One cohort was obtained from MSF-H in Northern Ethiopia

Indications of use

- Primary VL
  - HIV/VL
  - renal impairment
  - liver impairment
  - viral hepatitis
  - severe malnutrition
  - severe anaemia (Hb<5g/dL)
- Relapses

Initial treatment outcomes after AmBisome monotherapy (30mg/kg) in north Ethiopia

MSF-H treatment centre

Patient groups	Initial Cure n (%)
HIV negative, primary VL (n=94)	87 (92.6)
HIV positive, primary VL (n=116)	86 (74.1)
HIV positive, relapses (n=79)	30 (38.0)

Source: Courtesy of Dr. Ritmeijer K.

Treatment outcomes in VL patients treated with AmBisome

Experience from Kassab Hospital, Eastern Sudan, 2005 – to date

All patients had primary VL

- N treated: 42
- Doses: 30mg/kg (n=39)
  42mg/kg (n=3)
- Outcomes: cured (n=40)
  died (n=1)
  relapse (n=1)

Treatment outcomes in Primary VL patients treated with AmBisome

Experience from Gondar Hospital, north Ethiopia (2007-10)

Total dose	HIV status	Treatment outcomes (n)	
		Initial cure	Died during Tx
21mg/kg (n=26)	HIV neg	16	3
	HIV pos	4	-
	Unknown	-	3
28-35mg/kg (n=6)	HIV neg	-	-
	HIV pos	4	1
	Unknown	1	-
Total (n=32)		**25 (78%)**	**7 (22%)**

Conclusions

- Low-dose (5-15mg/kg) AmBisome appears to be highly effective in India
- Data obtained in East Africa are from a very heterogeneous population
- In East Africa, higher AmBisome doses are required to treat VL; insufficient data exist on its use as a first-line treatment
- 30mg/kg multiple dose AmBisome could be an effective treatment option against VL
- There is an ongoing RCT (LEAP 0106) on the minimum effective dose of AmBisome in Ethiopia and Sudan comparing single doses (7.5mg/kg-15mg/kg) versus a comparator of 21mg/kg (3mg/kg x 7 doses)

ACKNOWLEDGEMENTS

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