Two Drug Combinations for the Treatment of Visceral Leishmaniasis in the Indian Subcontinent

A Collaborative Research

Indian Council of Medical Research (ICMR)
&
Drugs for Neglected Diseases *initiative (*DND*i)*

Prof. Shyam Sundar (PI and Coordinating Investigator)

Dr Prabhat Sinha, PI, Rajendra Memorial Research Inst. RMRI, Patna (ICMR)

Why Drug Combinations?

Drawbacks of present treatments

- Recently available drugs are used as monotherapy: Risk of Resistant parasite
  - Amphotericin-B *30 days, i.v.; R = Low*
  - Miltefosine *28 days; R = High*
  - Paromomycin *21 days; R = High*
  - L-Amb *single or a few infusions*
- Allergic reaction *(non-immunological)*
- Non-responders
- Need for different treatment modalities

Objective & Rationale

- Objective:
  - Provide data to Authorities to make evidence-based recommendations for replacing monotherapy with combinations in the kala-azar elimination program of the Indian Subcontinent
- Rationale:
  - Shorten duration of treatment → lower side effects
  - Reduce cost of treatment (avoid need for DOTS)
  - Avoid emergence of resistance towards new drugs

Best Science for the Most Neglected

The Trial Design

A Definitive Randomized Non-Inferiority Controlled Trial: to detect a difference > -7% (97% vs. 90%) between combination therapy and standard treatment

Standard treatment: Ampho-B 1mg/kg/EOD for 30 days (15mg/kg)

vs.

1- AmB + Milt-7 (8 days)	**AmBisome (5mg/kg) + Miltefosine (50mg/day if <25 Kg, 100mg >25 Kg; or 2.5mg/kg for children <12 yrs)**
2- AmB + Paro-10 (11 days)	**AmBisome (5mg/kg) + Paromomycin (11mg/kg/day; (15mg paromomycin-sulfate)**
3- Milt-10 + Paro-10 (10 days)	**Miltefosine 10 days + Paromomycin 10 days**

Sample size N = (156x4) = 624

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Procedures and Definitions

- **Clearances: Institutional, ICMR, DCGI, Basel (Switzerland)**
- **Safety: AE - Clinical, Haemat. & Biochem. Others: Common Terminology Criteria (CTC)**
  - *http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm*
- **Efficacy: definitive cure = 6 months (-2 wks to + 6 weeks)**
- **ITT = All patients enrolled (N=634)**
- **PP = Patients who completed treatment and all follow-up visits (N=618)**
- **DCGI: First enrol 120 adults and evaluate results; then enrol all**
  - **(5- 60 years old)**

293 adults first, then 169 adult + 173 children

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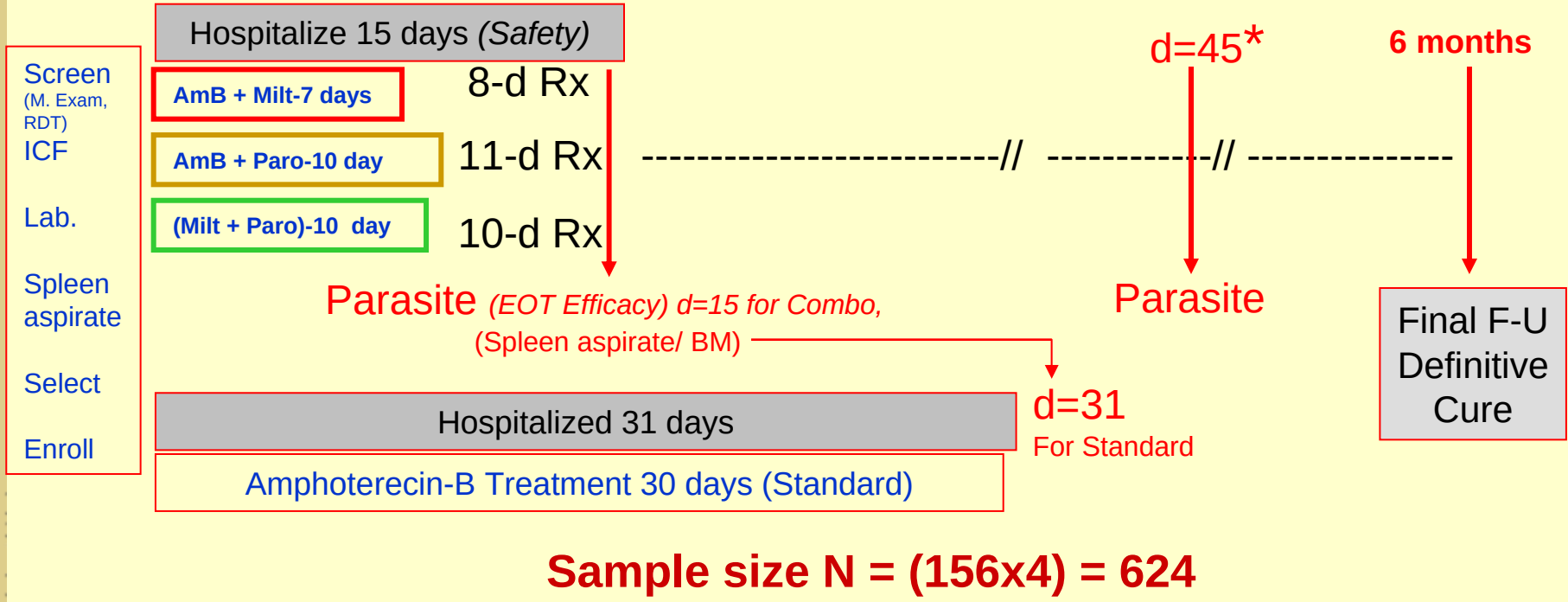

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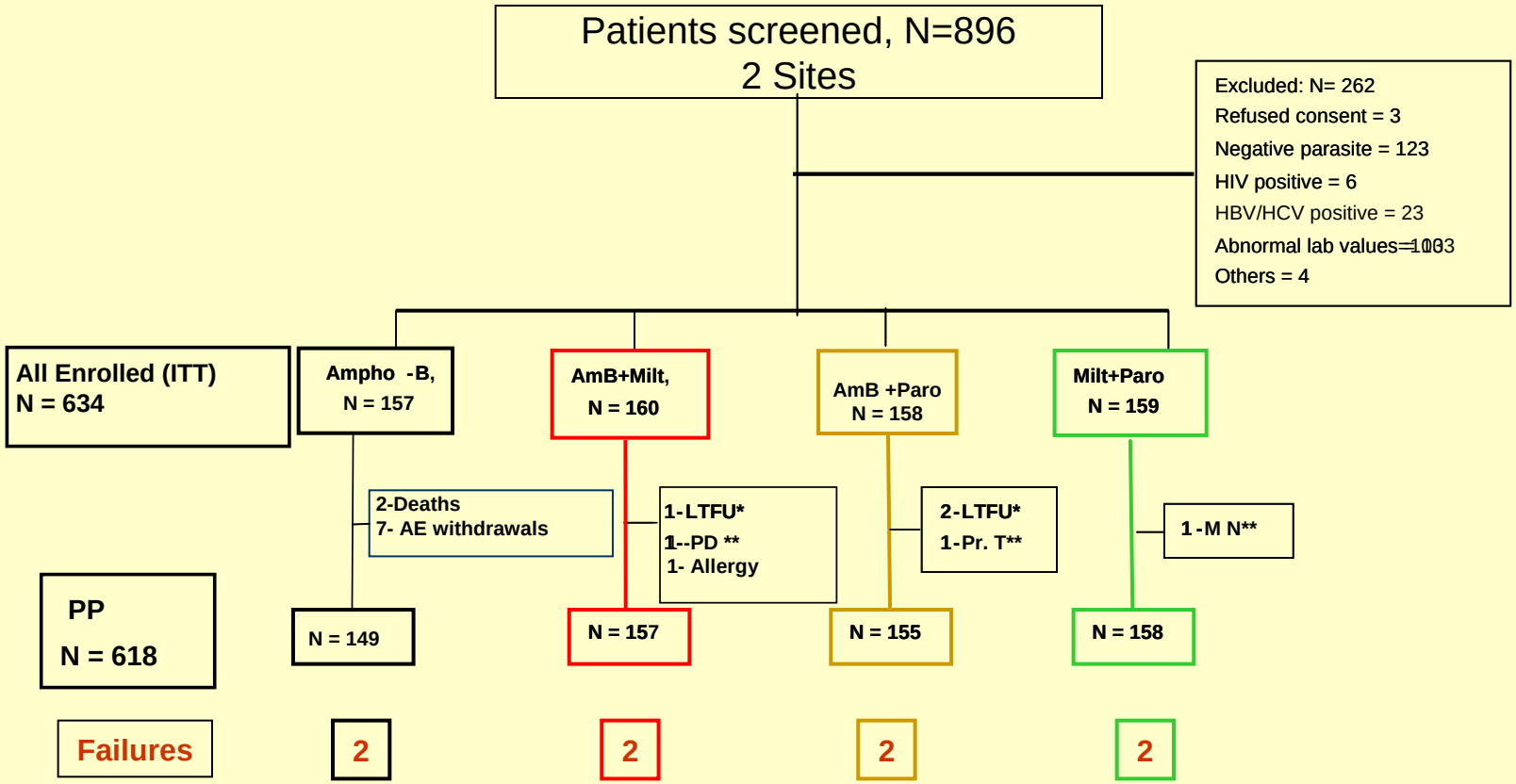

2 deaths: one related (cardiac infarct); one unrelated (car accident)
*Lost to follow up (LTFU)
**3 Protocol deviation:
1- Low dose of AmB in AmB+Milt
1- Pr. T = prothrombin time 5 sec higher than permissible in AmB + Paro
1- M N = malnourished child (BMI < 15) in Milt + Paro

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Table 2 Definitive Cure according to Treatment Groups at 6 mo's (-2wks + 6 weeks)

Definitive cure at 6 months	Ampho B (N=157)	AmB-5 + Milt-7 (N=160)	AmB-5 + Paro-10 (N=158)	Milt-10 + Paro-10 (N=159)
All Patients Randomized, ITT (N = 634)	157	160	158	159
No. Of patients Cured	146	156	154	157
Percent	**93.0%**	**97.5%**	**97.5%**	**98.7%**
95% CI	[87.50, 96.27]	[93.32, 99.20]	[93.24, 99.19]	[95.06, 99.78]
Per-protocol population PP (N = 618)	148	157	155	158
No. Of patients Cured	146	155	153	156
Percent	**98.6%**	**98.1%**	**98.7%**	**98.7%**
95% CI	[88.21, 96.71]	[94.12, 99.51]	[94.93, 99.78]	[95.03, 99.78]

Note: 8 patients who could not complete treatment due to AE & SAE during Ampho B treatment (considered "Failures") are excluded from the PP population

Differences of + 4.5 to +5.7% between combinations and Ampho B for ITT
-0.5% to +0.1% for PP. The non-inferiority (>-7% hypothesised) is established

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SAEs (related or possibly related to treatment) and AEs (related)

Variable	Ampho	AmB + Milt	AmB+Paro	Milt+Paro
	N=157	N=160	N=158	N=159
	n (%)	n (%)	n (%)	n (%)
Patients with at least one AE	143 (91.1)	83 (51.9)	73 (46.2)	72 (45.3)
SAEs reported	1 (death related)	1 (Allergy to test AmB)	0	0
Deaths	2 (one unrelated)	0	0	0
Discontinuations due to (S)AEs	8	1	0	0
AEs according to body system				
Cardiac Infarct (SAE)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Ascites (SAE)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	3 (1.9)	3 (1.9)	1 (0.6)	5 (3.1)
Vomiting	30 (19.1)	25 (15.6)	5 (3.2)	16 (10.1)
Asthenia	1 (0.6)	3 (1.9)	2 (1.3)	3 (1.9)
Chills	113 (72.0)	20 (12.5)	20 (12.7)	0 (0.0)
Injection site pain	0 (0.0)	0 (0.0)	10 (6.3)	14 (8.8)
Pyrexia	37 (23.6)	31 (19.4)	33 (20.9)	32 (20.1)

The Trial

- GCP training
- Ethical clearance from local institute, ICMR, DCGI; Basel (Switzerland)
- Monitoring (initially 2/month; later 1/month)
- Parasitology independent verification
- Audit by independent international auditor
- Independent data management and statistician
- Regular DSMB meeting
- Weekly report by GVK-BIO (CRO)
- Monthly report to DSMB
- Steering Committee (Mid-term) review

Progress toward implementation

Discussed at RTAG & WHO Expert Committee:

- Implement combination therapies as soon as they become available to prolong the efficacy of newly available drugs

Recommended at DCGI meeting:

- Conduct feasibility and cost-effective studies on combinations

Recommendation at a recent meeting with Authorities in India:

- Sb^{+v} should not be used
- Monotherapies with miltefosine and paromomycin are of long duration and subject to selection of resistant parasites; therefore, treatment strategy needs to be revised. Combination therapy has the potential of addressing these issues
- Liposomal Amphotericin B alone or in combination with other drugs should be used whenever feasible
- A pharmacovigilance network needs to be set with the current infrastructure by appropriate training and tools to monitor side effects
- Monitor drug resistance now and when combination is introduced in the control program

DNDi, TDR and iOWH planning an implementation project using the new modalities of VL treatment

Treatment of VL using drug combination

(A Collaborative Study)

Prof. *S. Sundar* et. al. KAMRC: Muzaffarpur*

Dr P. K. Sinha et. al. RMRIMS, Patna

DSMB:
P. Smith,
C.P. Thakur, N.K. Arora, R.M. Pandey

Independent parasitology audit
A. Moody

Independent Auditor:
Rita Walt Consulting GmbH,
Schaffhausen, Switzerland

Michel Vaillant, (Statistician)
GVK-BIO (CRO) Gurgaon
Gilead (Contributed AmB)

Ethical Committees:
Institutional, ICMR, DCGI,
Basel (Switzerland)

Steering Committee: DG, ICMR, Dir. RMRI (P.Das), WHO, SEARO (S. Bhattacharya) , HQ (J. Alvar), TDR (P. Olliaro), Rep. MoH & Local Experts,

DNDi Team: Farrokh Modabber
Bhawna Sharma (Head DNDi, India Office)
Sally Ellis, Manica Balasegaram,
Nathalie Strub-Wourgaft (Clinical Dir)
Shing Chang (R&D Dir.)
Bernard Pecoul (Ex. Dir)

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Thank you

Variable	Ampho B (N=157)	AmB-5 + Milt-7 (N=160)	AmB-5 + Paro-10 (N=158)	Milt- 10 + Paro-10 (N=159)	p-value
Age Yr Range - Yr ≤ 18yr - %	 28 ± 14 6 - 60 41	 27 ± 13 6 - 58 39	 25 ± 14 5 - 58 45	 28 ± 16 6 - 60 46	0.22#
Male sex- no. (%)	98 (62)	117 (73)	100 (63)	107 (67)	0.15**
KAMRC site - no. (%)*	119 (18.8)	120 (18.9)	119 (18.8)	120 (18.9)	
RMRI site - no. (%)*	38 (6.0)	40 (6.3)	39 (6.1)	39 (6.1)	0.99**
Patients with history of prior treatment (>45 days before enrollment	3	2	3	0	
Splenic aspirate score	2.2 ± 1.1	2.2 ± 1.2	2.1 ± 1.0	2.1 ± 1.1	0.37#
Weight - (kg)	40.5 ± 11.7	40.5 ± 11.3	39.0 ± 11.7	39.9 ± 12.1	0.62#
Spleen size - (cm) below left costal margin	5.0 ± 3.3	5.0 ± 3.6	6.0 ± 3.8	5.0 ± 3.2	0.10#
Hemoglobin - (g/dl)	8.1 ± 1.7	8.4 ± 1.7	8.2 ± 1.9	8.3 ± 1.9	0.58#
White-cell count (per µl(med,(min;max)))	2,900 (1,100;7,900)	2950 (1,100;12,400)	3100 (1,100;15,700)	3,000 (1,100;19,000)	0.32#
Platelet count (per µl) (med,(min;max))	112,000 (43,000;578,000)	117,000 (41,000;601,000)	110,000 (41,000;599,000)	110,000 (40,000;678,000)	0.54#
Creatinine - (µmol/L/)	71 ± 11	73 ± 11	72 ± 11	72 ± 11	0.39#
Blood urea nitrogen - (mg/dl)	23 ± 8.3	22 ± 8.2	23.9 ± 8.7	23.1 ± 7.9	0.22#
Alanine aminotransferase- (U/L; (med,(min;max))	31 (8;129)	34 (4;121)	30 (5;123)	33 (5;153)	0.15#
Aspartate aminotransferase (U/L; (med,(min;max)))	48 (14;106)	49 (11;114)	45.6 (8;111)	48 (14;109)	0.32#

* Percentage of total number of patients enrolled

** p value is computed using chi-square test.

p value is computed using ANOVA.

Available drugs for VL (Indian subcontinent)

Drug	Pentavalent Antimonials	Amphotericin B	Liposomal Amphotericin B	Miltefosine	Paromomycin
Dose/Duration	20 mg/kg/day 28 days	1 mg/kg e.o.d. (15mg/Kg total) 30 days	3-5 mg/kg/infusion (15-20 mg/kg total) 5-10 days Single 10mg/kg	1.5-2.5 mg/kg/day (India only) 28 days	11 mg/kg/day (India only) 21 days
Administration	iv or im	Slow iv	Slow iv	Oral	im
Efficacy	35-60%	~ 97% all regions	> 95%	85-95%	90-94%
Resistant Parasite	Up to 60% (Bihar, India)	Not documented	Not documented	Lab isolates	Lab isolates
Toxicity	+++ Cardiac toxicity pancreatitis nephro –hepato toxicity, pain	+++ Nephrotoxicity Rigors and chills during infusion vomiting	+/- Rigors and chills during infusion	++ Gastro-intestinal Nephro/ hepato tox Teratogenic in animals	+ Nephrotoxicity ototoxicity Pain at injection site
Price	SSG ~$50 Glucantime ~ $70	Generic price: ~ $49	Preferential price: US$ 126-252 for 10-20 mg/kg Commercial price: ~10x more	Preferential price: ~ $74 Commercial price: ~ $150	~ $10
Problems	Length of Rx Painful injection Toxicity Resistance	Length of Rx Toxicity Heat stability i.v. infusion	Price Heat stability (Store <25° C) i.v. infusion	Length of Rx Price Teratogenicity Imminent resist. Compliance	Length of Rx Pain Compliance Resistance