Safety and Effectiveness of new treatment regimens for visceral leishmaniasis in Bangladesh and India

DNDi
Drugs for Neglected Diseases *initiative*

RMRIMS - Patna

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MEDECINS SANS FRONTIERES

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Introduction

New treatment regimens developed only in the last few years from already existing drugs for VL, specifically - AmBisome®, paromomycin and miltefosine

These new treatment modalities have now been recommended by WHO Expert Committee on the control of leishmaniasis (March 2010) and RTAG (WHO SEARO)

DNDi conducted 2 studies on combination treatments and Ambisome monotherapy:

- Phase 3 clinical trial in Bangladesh (safety and efficacy)
- Pilot implementation study in India (safety and effectiveness)

<u>Objectives:</u>
Provide data for authorities to make evidence-based recommendations for replacing Miltefosine monotherapy with ambisome and combination therapies in the National kala-azar Elimination Program

<u>Rationale:</u>
Reduce duration & side effects, improve compliance and also prevent emergence of resistant parasites (increase duration of effectiveness of available drugs)

VL Bangladesh combination trial

Ethical Clearance: ICDDR,B BMRC

A Phase III, open label, randomized, non inferiority study conducted (2010-2014)
Milt (2.5mg/Kg/d) + PM (11mg/Kg/d) for 10 days
AmB (5mg/kg SD) + Milt (2.5mg/Kg/d) for 8 days
AmB (5mg/Kg SD) + PM (11mg/Kg/d) for 11 days,
compared to: AmB (5mg/Kg on Days 1,3 and 5, total dose of 15mg/kg)

PROJECT DESIGN

Step 1	Step 2	
Community Based Medical College, Mymensingh	3 Upazila Health Centres n=482	
120 patients enrolled	Trishal	218
	Bhaluka	67
	Gafargaon	197

Results – Bangladesh study (n=601)

	Ambisome	AmB+PM	AmB+Milt	PM+Milt
Number of patients (n=601)	158	159	142	142
Initial cure at D45 – n(%)	155 (98.1)	158 (99.4)	134 (94.4)	139(97.9)
Final Cure at 6 month n(%)	155 (98.1)	158 (99.4)	134 (94.4)	139 (97.9)

Adverse Events

	AmBisome (158)	AmB+PM (159)	AmB+Milt (142)	PM+Milt (142)
Total adverse events reported	310	320	329	318
Total no of subjects with adverse events n(%)	95 (60.1)	97 (61)	86 (60.6)	90 (63.4)
Drug Related Serious Adverse Events (n=4)	0	0	1	3
Non-Drug Related Serious Adverse Events (n=8)	3	1	4	0

Death: 03- All not related to study drug

All other SAEs (Related and Non Related) were resolved

Conclusion

- All treatments showed excellent safety and efficacy
- These new treatments can be safely administered at Upazhala level
  - Shorter treatment duration
  - Better compliance
  - Less side effects
- Combination regimen to be choice of treatment at sites where cold chain cannot be deployed as in case of Ambisome treatment.

Pilot Implementation Study - India

Ethical clearance: RMRIEC, MSF-ERB, LSHTM

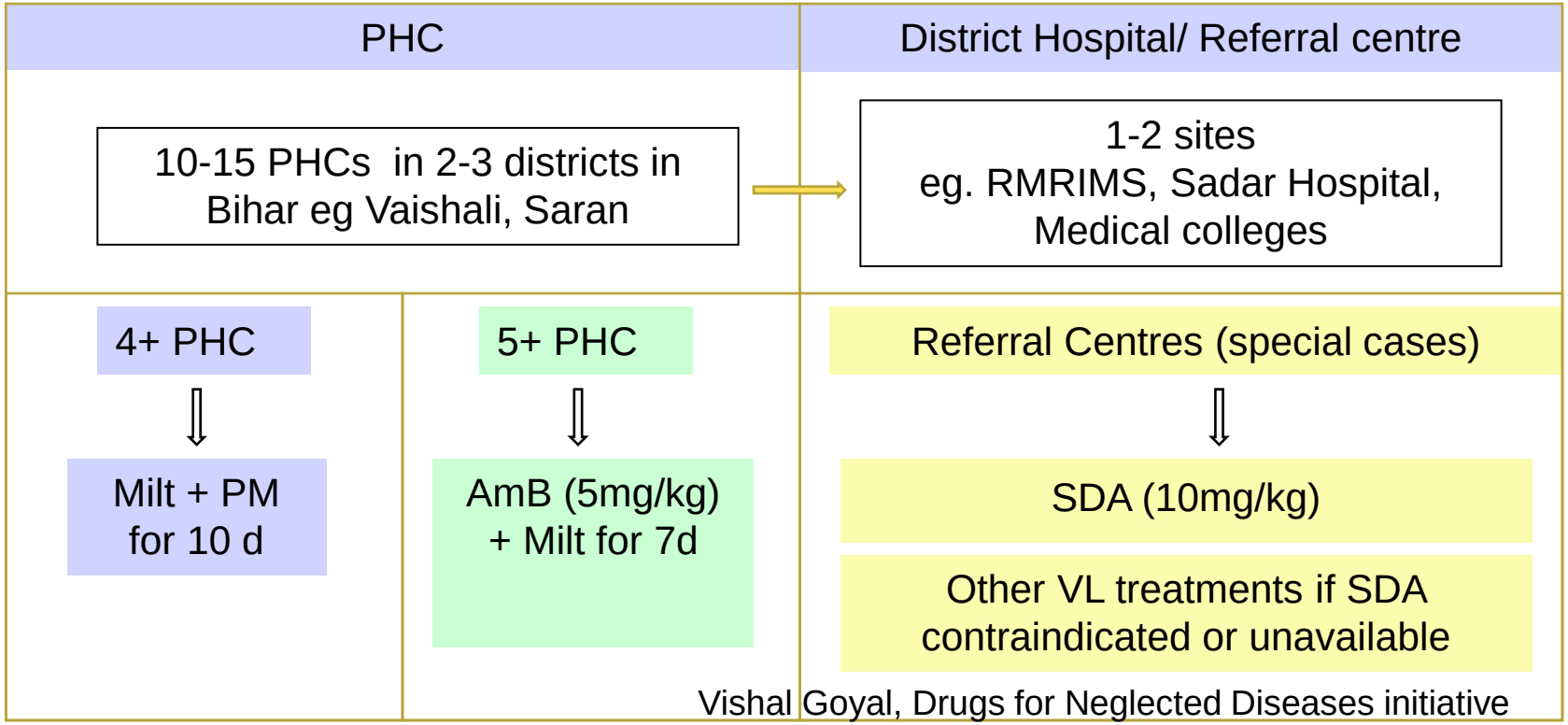
Open label, prospective, non randomised, non comparative, multicentre study in public health sector 2012-2015

Single Dose Liposomal Amphotericin B (Ambisome) 10mg/kg

Milt (2.5mg/Kg/d) + PM (11mg/Kg/d) for 10 days

AmB (5mg/kg SD) + Milt (2.5mg/Kg/d) for 8 days

PROJECT DESIGN



Objectives

- Determine **under field conditions**
  - **effectiveness,**
  - **safety profile**
- Provide **evidence based recommendations** for policy makers

Results – India study (n = 1761)

	SD AmB	AmB+MF	MF + PM
Number of patients started on treatment (n=1761)	892	357	512
Initial cure at day 10 (%) (95% CI)	885 (99.2%) (95%CI-98.6-99.8)	354 (99.2%) (CI-98.3 – 100.0)	508 (99.2 %) (CI-98.4- 99.9)
Number of patients completed 06 Month FU (n=1591)	828	331	432
Final Cure at 06 Month n (%)	768 (93%) (CI-91.3-94.8)	296 (89.4 %) (CI-86.1-92.7)	421 (97.4 %) (CI-95.9-98.9)
Number of Relapse (n)	37 (4.5%)	16 (4.8%)	2 (0.5%)
Number of patients completed 12 Month FU (n=788)	349	183	256

12 month follow up yielded additional 6 relapse in SDA, 6 relapse in A+M and 5 PKDL cases in M+P arm

Adverse Events

	SD AmB	LAmB + MF	MF + PM
Total Adverse Events Reported	159	137	121
Total no of subjects with adverse events n(%)	120 (13.5)	90 (25.2)	90 (22.4)
Drug Related Serious Adverse Events n(%)	2* (0.5)	0 (0)	0 (0)
Non-Drug Related Serious Adverse Events n(%)	3** (0.7)	0 (0)	0 (0)

* Allergic reaction + Atrial ectopic. Both resolved

** Pneumonia, Empyema, Urinary Tract Infection. All resolved

Limitations

- Children **not** treated at Primary Health Centre level and treated at District Hospital only as per regulatory recommendation

- Higher number of severely complicated patients treated in one arm, that is single dose Ambisome arm

Conclusion and recommendations

- All treatments (except Amb + MF) showed excellent safety and effectiveness within public health sector

- Indian National program revised policy in Sep 2014
  - Single Dose Ambisome as first option
  - Combination as second option

- Combination regimen to be choice of treatment at sites where cold chain cannot be deployed
- Establishment of Active Pharmacovigilance at sentinel site is recommended

Lessons learnt

- 3 Combination regimens and SDA are safe and effective treatment in public health sector at field level and feasible to implement at large scale in both countries
- Relapses continue to occur after 6 month post treatment, need to Follow up patients for 12 month to generate evidence on relapse
- Cohort Event Monitoring should be strengthened at all sites in India and Bangladesh to document long term outcome data
- Committed field workers for follow up activity ensuring minimal LTFU

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THANK YOU

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Vishal Goyal, Drugs for Neglected Diseases initiative