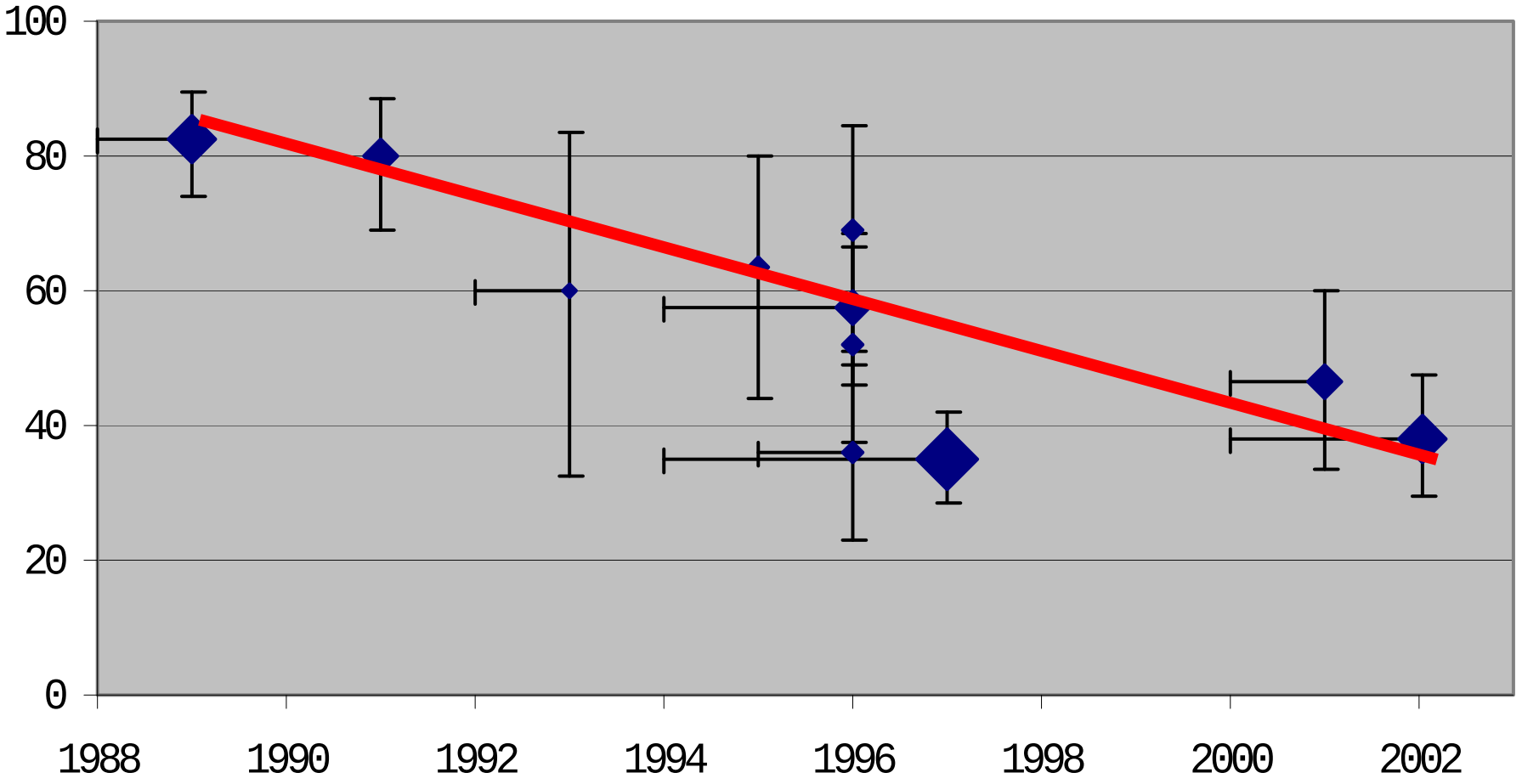
Needs and Challenges in Developing a New Treatment for Visceral Leishmaniasis

Shyam Sundar, MD
Professor of Medicine
Institute of Medical Sciences
Banaras Hindu University, India

TREATMENT OF VISCERAL LEISHMANIASIS

Efficacy of SSG 20mg/kg/d in Bihar, India during 1988-2002.



Amphotericin B

- Polyene antibiotic (Amphotericin B deoxycholate)
- Dose 0.75-1.0 mg daily or alternate days for 15-20 infusions
- Expensive & needs hospitalisation for 4-5 weeks
- Infusion reactions, thrombophlebitis common
- Hypokalemia, myocarditis & death are serious, but uncommon, toxicities
- High Cure rates ~100%
- Used as first line drug in Bihar with areas of Sb resistance

Single Dose Liposomal Amphotericin B (AmBisome) in Indian Kala-azar

Total Dose mg/kg	No. of Patients	Treat. Dur.	Cure Rate
5	46	1	91 (Sundar, BMJ,2002)*
5	45	5	93
7.5	203*	1	90 (Sundar, CID, 2003)*
15	17	1	100 (Thakur, AAC, 2001)

*** Multicenter**

Liposomal Amphotericin B - AmBisome

- Total dose – most important determinant in the outcome – Total dose requirement
  - 20-24 mg/kg - for Brazil and Europe
  - 18-20 mg/kg – for Africa
  - 15 mg/kg – for Asia
  - 40 mg/kg for Immunosuppressed
- Even after a remarkable 90% decrease in the price of AmBisome, access remains a problem
- Problem of cold chain

Paramomycin (Aminosidine)

- An aminoglycoside (parenteral)
- Good antileishmanial activity, earlier used for bacterial & Parasitic infections
- In several phase II studies 16 mg/kg for 3 weeks cured 93% VL patients
- Has been licensed recently after results of Phase III trial became available (Cure rate 94.6%)
- Safe, Good alternative to antimony as first line Tt
- Produced in India, cheap(10 US$ per treatment course)
- Injectible (3 weeks)
- Being aminoglycoside, vulnerable for resistance

Miltefosine

- Hexadecylphosphocholine (alkyllphospholipid analogue)
- Developed as an oral antineoplastic agent, but GI adverse events limited its use
- Excellent antileishmanial activity in experimental animals and in vitro
- A pilot dose escalating study conducted in 1997

(Sundar et al, Lancet, 1998)

Miltefosine

- Dose: 100 mg (≥25 kg); 50 mg (<25 kg); Children 2.5mg/kg
- Duration: Four weeks , Oral administration - big advantage
- Side – effects:
  - Vomiting occurs in ~40%
  - diarrhea in ~20%.
  - Transient elevation of hepatic enzymes
  - Skin allergy, nephrotoxicity are occasionally seen
- Long term cure rates 94%
- Cannot be used in pregnant females [teratogenic], and those refusing contraception (for the treatment period and another three months) *(Sundar et al, NEJM, 2002)*

Summary

- In Indian subcontinent -Miltefosine as a therapeutic tool for ELIMINATION programme (by 2015)
- Pros and Cons
  - Orally administrable
  - Promising efficacy (Cures Sb refractory patients also)
  - However, there are challenges…

<u>There is a need to revisit the current strategy</u>

Multidrug Treatment of VL - Rationale

- Every drug with the exception of amphotericin B is prone to development of resistance
- No new drug in pipeline
- The only way to protect the newly developed drugs is to develop combination chemotherapy
  - Shorten duration
  - Better compliance
  - Reduce cost
  - Less chances of development of drug resistance
  - Reduce drug pressure; mutual protection against resistance → prolong therapeutic life-span of effective use

Experimental Evidences of Combinations (Siefert & Croft, 2006)

- Activity enhancement indeex (AEI)
  - In vivo
    - Miltefosine + Ampho B – 11.3
    - Miltefosine + Paromomycin – 7.2
    - Miltefosine + SAG – 2.38
- Thus, the three approved drugs for VL can be tried for multidrug therapy
    - AmBisome + Miltefosine
    - AmBisome + Paromomycin
    - Paromomycin + Miltefosine

VL Combination Toxicology

Combination drug administration (DNDi/Advinus Therapeutics, Bangalore)

Study groups

- Miltefosine alone
- AmBisome alone
- Paromomycin alone
- Paromomycin + Miltefosine
- AmBisome + Miltefosine (concomitant 5 days, milt alone 23 days)
- AmBisome + Paromomycin (concomitant 5 days, paromo alone 23 days)

Results

- No significant haematological changes: alone vs combined
- No significant clinical chemistry changes: alone vs combined

Results of a Phase II combination trial in Indian VL (CID, In press)

Regimen	n	Initial Cure Rate (%)	Final Cure Rate	95% Confidence Interval
AmBisome (5mg/kg)	45	100	91.1	78-97
AmBi 5 + Milt 14 days	45	100	95.6	84-98
AmBi 3.75 + Milt 14 days	45	100	95.6	84-98
AmBi 5 + Milt 10 days	46	100	97.8	87-100
AmBi 5 + Milt 7 days	45	100	97.8	87-100

Summary:
What Are the Therapeutic Options ?

- Use Antimony only in responsive regions, toxic drug, treatment related mortality in >5% patients, try and replace it quickly
- Amphotericin B – Use only as rescue/2nd line drug
- Liposomal AB – very attractive but cold chain?
- Miltefosine – Alone is a poor choice. DOT, lab monitoring, cotraception
- Paromomycin – 21 daily inections, potential for resistance
- More drugs needed, nothing in clinical development

Combination Chemotherapy with short duration regimens?

Challenges to access

- Major challenge is to translate these research fruits into field setting
- For example **miltefosine**
  - Teratogenic (how to deal with women of child bearing age group),
  - Long half life (rapid emergence of resistance)
  - Uninterrupted availability?
  - Compliance in domiciliary care ? (DOT)
  - Availability in private sector
  - In a recent evaluation we found 20-33% patients discontinued therapy
  - Real danger of loosing this important drug in next few years
- Paromomycin
  - 21 daily injections (What can be done for compliance)
- How to monitor the efficacy and adverse events