Leishmania Vaccine Development: Progress and challenges in the context of other control strategies

Farrokh Modabber, Ph. D.  
Senior Advisor, Leishmaniasis
Decreasing SSG efficacy for VL treatment

Efficacy of SSG 20mg/kg/d in Bihar, India during 1988-2002.
Lots happened for VL management

1. New drugs & treatments: Miltefosine, Injectable Paromomycine, AmBisome, Drug combinations

   Most significant advance:
   **Single-dose 10mg/Kg AmBisome for visceral leishmaniasis in India.**
   Cure rate after 6 mo FU: **95.7%** (95% CI, 93.4 to 97.9)

Yes, Can be used in rural hospitals in Bangladesh 97% cure rate, No SAE

*Dinesh Mondal, et.al. www.thelancet.com/lancetgh
http://dx.doi.org/10.1016/S2214-109X(13)70118-9*

Cost negotiated by WHO-MSF and Gilead to about $120/typical patient

Local production in India, to be improved and may create competitive pricing
### Drug Combination for VL (DNDi Trial)

<table>
<thead>
<tr>
<th>Treatment: Drug Combination Trial</th>
<th>Ampho-B 30 days in Hospital 15 injections</th>
<th>AmB 5mg/Kg x1 + Paro. 10X (11 days)</th>
<th>AmB 5mg/Kg x1 + Milt. X 7 (8 days)</th>
<th>Paro. 10x + Milt. X 10 (10 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final cure (ITT) 95%CI 97.5%</td>
<td>93.0%</td>
<td>97.5%</td>
<td>97.5%</td>
<td>98.7%</td>
</tr>
<tr>
<td>FU 6 months</td>
<td>87.5, 96.3</td>
<td>93.3, 99.2</td>
<td>93.2, 99.2</td>
<td>95.1, 99.8</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Strategy</th>
<th>Drug cost</th>
<th>Other direct medical</th>
<th>Non-medical &amp; indirect</th>
<th>Total cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-AmB + MF</td>
<td>95.7</td>
<td>14.8</td>
<td>12.8</td>
<td>123.4</td>
</tr>
<tr>
<td>L-AmB + PM</td>
<td>87.1</td>
<td>20.5</td>
<td>25.3</td>
<td>132.9</td>
</tr>
<tr>
<td>MF + PM</td>
<td>29.5</td>
<td>19.5</td>
<td>23.8</td>
<td>72.9</td>
</tr>
<tr>
<td>L-AmB 10</td>
<td>140.0</td>
<td>11.0</td>
<td>2.5</td>
<td>153.4</td>
</tr>
<tr>
<td>SSG</td>
<td>57.8</td>
<td>40.7</td>
<td>73.4</td>
<td>171.8</td>
</tr>
</tbody>
</table>

**Not as efficacious in Africa.**
WHO recommend: SSG + Paromo
Trial supported by DNDi – done by Leish E. Africa Platform
2. Commitment to eliminate VL (<1/10,000) in India, Nepal & Bangladesh by 2015? (availability of drug and diagnostic; daily payments to hospitalized patients in India, vector control; awareness, etc.

3. Serious drug development program for VL (DNDi with major Pharma). NCE’s identified and being developed

4. Significant reduction in incidence of disease in major foci, India, Bangladesh, Nepal, Sudan, Kenya, Ethiopia, Uganda (LEAP), Brazil
Factors responsible for decline:
- Natural cycle (trough – unknown reasons)
- Impact of treatments (Miltefosine, AmBisome) MSF, National Prog.
- Elimination program: payment to patients, vector control
Reduced Incidence of VL in High endemic Foci

Bangladesh:
75/100 upazilas achieved <1 case/10,000  2012
40/100 Upazila reported 0 case till Aug. 2013
Shah Golam Nabi, Programme manager, DGHS, Mohakhali, Dhaka).

Nepal: Yearly reduction in incidence, lately ± 200/yr

East Africa: > 50% reduction in cases
mortality highly reduced

1995-2005 LEAP countries (Sudan Kenya, Ethiopia, Uganda) had 40,000 VL cases/year (20,000 from Sudan)
with a mortality of about 4000 cases/year
In recent years there are less than 50% with very low mortality (Head of LEAP, Dr A. M. Musa).

Vector control is controversial, but here a Demonstration project
Community-based insecticide impregnated Bed net.
Mondal, et al.’s EID Journal:
Volume 19, Number 7—July 2013
Cutaneous Leishmaniases (CL) A neglected among Neglected Diseases – No Progress!

Estimated 1,500,000 cases / year
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Past: First Generation Vaccines (Prophylaxis)

Killed parasites with or w/o BCG → Safe but no prophylactic efficacy

Addition of alum: (Alum-ALM+ BCG →↑ CMI, not Ab!

One Phase-2 prophylactic trial in Sudan against VL:
  544 randomized to single injection of Alum-ALM+BCG or Diluent.
  2 year Follow up:
  0 case in Vaccinated vs 4 in control
(Needed more studies, but not continued)
Issues: Use of FCS to grow parasite, Standardization & BCG lesions, …
IDRI Vaccines: Prophylactic and therapeutic efficacy in mice against challenge by needle but not by sandfly (C57 Bl), protective in Balb/c. Safe and Immunogenic (Phase-1 trials in US and India).

Trials in Colombia, Brazil (CL), Peru (ML), *Accelerated time to cure in CL and ML patients when used in combination with chemotherapy*

Trials against PKDL & DCL showed *No therapeutic efficacy* with or without chemotherapy.

New vaccine focused on VL: KSAC+ GLA - SE being developed

**Is a TLR-4 agonist a good adjuvant for human leishmaniasis??**

In mice, CpG (TLR-9 agonist) enhances MPL-SE activity
York University - Adenovirus vector with 3 genes of *Leishmania*
Phase-1 completed, awaiting further trial (Prof. Paul Kaye)

**ChAd63-KH: a new therapeutic vaccine for VL / PKDL**

*Program PI: Paul Kaye*

**The insert....**
- KMP-11
- synthetic HASPB
  - Engineered to reflect strain diversity in SE Asia/E. Africa

**The viral vector....**
- ChAd63
  - produced in suspension culture Procell 92 cell line for scalable manufacture
  - Safety and immunogenicity data available from hundreds of volunteers

**Preclinical proof of concept....**

**The clinical trial....**
- **Phase 1** -in-human study: dose escalating, “prime only”
  - Excellent safety profile confirmed
  - Excellent levels of CD8+ T cell responses (breadth / magnitude / % responders)
LEISHDNAVAX
Prevention and therapy of all forms of leishmaniasis
(Provided by Dr Christiane Juhls, Mologen on behalf of Consortium)

Vaccine: No clinical studies yet
Mixture of 5 highly conserved, highly immunogenic Leishmania antigens encoded by small minimalistic linear DNA expression vectors

Ready to enter clinical Phase 1 trial:

✔ Preclinical efficacy and safety proven
✔ CD4 and CD8 T cell responses against all 5 antigens detected in target populations
✔ Clinical sites (VL, India & CL, Tunisia) selected, study plan outlined, clinical immunomonitoring established
✔ Indian pharmaceutical partner identified

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Efficacy and dose-response in murine VL model
Parasite load in liver, 3 weeks post challenge

S. Das, S. Roy, IICB Kolkata
Vaccine or Immune Res. Modifiers (IRM) for Therapy

- Used in therapy (Convit et. al. Venezuela in thousands of patients)

- Alum-ALM+ BCG + antimonial on persistent PKDL, difficult to treat with drugs alone. PoC trial.

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug alone</th>
<th>Drug + Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>8/15 (53%)</td>
<td>13/15 (87%)</td>
</tr>
<tr>
<td>180</td>
<td>6/15 (40%)</td>
<td>15/15 (100%)</td>
</tr>
<tr>
<td>(Final)</td>
<td>2 relapsed</td>
<td>All cured p&lt;0.004</td>
</tr>
</tbody>
</table>


Can also be used to reduce dose of drug

Machado—Pinto J. et al. *Int. J. Dermatol.* **41**:73-8, 2002

Mayrink’s vaccine registered as adjunct to low–dose antimony in Brazil, but not used
Situation: Increased resistance to Antimonials, (R-L.tropica isolated)

Increased incidence due to war, population displacement

Other control measures have failed

No acceptable, affordable and safe treatment is available
AmBisome, Miltefosin (costly, variable results), thermotherapy, … Unsatisfactory

Need vaccine and Immune Response Modifier to enhance cure: to shorten time to cure, reduce scars.

Opportunities:


2- Live challenge to evaluate vaccines (needle infection standardized for L. major, can be done in certain foci (without HIV)
Immune Response Modifier as Adjunct to Therapy


Can CpG ODN be used to treat established L. major skin lesions?

- 4-6 macaques per group challenged with 10⁶ metacyclic promastigotes
- Treated 15 days after challenge with 500 ug CpG ODN ID or SC (0.5mg/kg).

POC: D35 reduces the severity of a Leishmania amazonensis infection

Note: Lesion size of D ODN treated animals was significantly reduced when compared to saline treated controls or macaques treated with a different ODN sequence (p < .03, N=6/group).

Daniela Verthelyi, et. al.

FDA

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Seed Bank & Stabilates from well characterized *L. major*

**Iran**

18 volunteers injected with live *L. major* followed for 1 year

All developed lesion and all lesions healed

Mean duration to scar formation = 166.6 days (SD = 67.65)

14 recovered Volunteers injected again + 4 new volunteers

14/14 protected no ulcer = 100% protection
4/4 developed lesion, healed in 142.00 days (sd=88.30)

In larger Leishmanization programs, there were 2-4% reinfection.
About 50/1000,000 developed non-healing (recorded).

**Natural infection**
Vaccine Needs

• **For VL** *Short term:* Implement available control measures
  
  *Long term:* An affordable field friendly safe live vaccine: Much like BCG, smallpox vaccine

• One candidate: Live attenuated (i.e. p27-KO *L. donovani*, *Nakhasi, Fujiwara et al.* Better than registered vaccine for dogs.

• Consider cost of development and implementation for all vaccines.

• **For CL,** Vaccine is urgently needed, since there are no effective control measures. Use leishmanization as challenge to evaluate candidate vaccines quickly & cost-effectively. (must be done with caution in HIV-free foci). All participants are protected either by candidate vaccines or leishmanization.
THANK YOU
For Discussions
vaccine requirements

Anti-infection, anti-disease

How many injections, annual booster?

Dead vs. live vaccine: p27-KO (Attenuated) *L. donovani*, (H. Nakhasi, Fujiwara et al.)

Live challenge? Leishmanization for CL, *L. donovani* (Rescue with Ambisome)???

Therapeutic, vs. Prophylactic

Broad spectrum (Anthroponotic CL, Zoonotic CL).

Can Canine vaccine protect humans. P-27 KO was better than commercial dog vaccine

Cost of development & cost of implementation vs other control measures
<table>
<thead>
<tr>
<th>VL cases</th>
<th>Reported</th>
<th>Estimated</th>
<th>Population at risk/Total (Mil) (fm guesstimate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. America</td>
<td>3668</td>
<td>4500- 6800</td>
<td>20-40 / 597</td>
</tr>
<tr>
<td>East Africa</td>
<td>8569</td>
<td>29400-56700</td>
<td>15-20 / 214</td>
</tr>
<tr>
<td>Mediterranean Region*</td>
<td>875</td>
<td>1200-2000</td>
<td>25-40 / 370</td>
</tr>
<tr>
<td>West-Central Asia (M.E.)*</td>
<td>2496</td>
<td>5000-1000</td>
<td>20-40 / 442</td>
</tr>
<tr>
<td>Indian Sub-continent</td>
<td>42623</td>
<td>162100-313600</td>
<td>200-350 /1418</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>200,000</td>
<td>280 / 3041</td>
</tr>
</tbody>
</table>

**Cost of Treatment**

\[ \text{Cost of Treatment} = \$200 \times 200,000 \times P = 40 \text{ M} \]

**Cost of vaccination**

\[ \text{Cost of vaccination} = \$5/\text{dose} \times 2 \text{ inj for 28M} = 280 \text{ M}^{**} \]

* L. infantum/chagasi

** Assuming 100% protection with 2 injections in 10% of population at high risk


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