Combination therapy for visceral leishmaniasis

Why, what, where?

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VL treatment: main options

- Antimonials (SbV)
- Paromomycin (PM)
- Amphotericin B (AmB)
- Liposomal-Amphotericin B (L-AmB)
- Miltefosine (MF)
Why combination therapy?

- Efficacy
- Toxicity
- Compliance
- Duration of therapy
- Cost
- Resistance
  - SSG
  - MF
    - only oral drug
    - long half-life: risk of resistance
Previous research on combination therapy in Asia

- \( \text{Sb}^\text{V} + \text{PM} \) (3 RCT, India)
  - \( \text{Sb}^\text{V} \) 28 days
  - PM 21 days
  - \( \text{Sb}^\text{V} + \text{PM} \) 21 days
- \( \text{Sb}^\text{V} \) only ineffective, PM single or in combination effective
- PM 15 mg/kg recommended dose

Thakur et al, 1998-2000
Previous research on combination therapy in Asia

- **L-AmB**
  - 5-7.5 mg/kg sd: ~90% efficacy

  Sundar et al, BMJ 2001/CID 2003

- **MF**
  - 28 days treatment: ~95% efficacy
  - 14 days treatment: ~89% efficacy

  Sundar et al, NEJM 2002/CID 2000
90% of VL global burden

12 million people infected
350 million people at risk

2 million new cases each year
(1.5 million for CL and 500,000 for VL)

Under-reported
HIV co-infection

Visceral
Cutaneous / Mucocutaneous
- Phase II, non-comparative RCT, India
- N=45/arm; > 12 y

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Success Rate</th>
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<tbody>
<tr>
<td>L-AmB 5 mg/kg sd</td>
<td>91%</td>
</tr>
<tr>
<td>L-AmB 5 mg/kg + MF 14 days</td>
<td>98%</td>
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<tr>
<td>L-AmB 5 mg/kg + MF 10 days</td>
<td>96%</td>
</tr>
<tr>
<td>L-AmB 3.75 mg/kg + MF 14 days</td>
<td>96%</td>
</tr>
<tr>
<td>L-AmB 5 mg/kg + MF 7 days</td>
<td>98%</td>
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Sundar et al, CID 2008
Planned research on combination therapy in Asia

- WHO/TDR-sponsored trials- Phase II
  - L-AmB 5 mg/kg sd + MF 14 days
  - N=150 (2-65 years)
- India
  - Started Oct 2008
  - Results expected in 2010
- Bangladesh
  - Planned
VL-Combo Asia (DNDi)

- Phase III, non-inferiority trial
- India
  - Started 06/2008; children planned
  - Results expected early 2010
- Bangladesh/Nepal
  - Start 2009; Results 2010

- L-AmB 5 mg/kg sd + PM 15 mg/kg 10 d
- L-AmB 5 mg/kg sd + MF 7 d
- MF + PM 15 mg/kg 10 d
- AmB 1 mg/kg 15x/30 d
Ongoing research on combination therapy in Africa: LEAP-0104A/B (DNDi)

- Phase III, non-inferiority trial
  - Kenya, Sudan, Ethiopia, Uganda
  - LEAP0104A: start 2004
    - High failure rate with PM 15 mg/kg in certain sites (Sudan)
      - Pharmacokinetics? Parasite strain?
  - LEAP0104B with PM 20 mg/kg
  - Results early 2010
Combination therapy in Africa: experience with MF and L-AmB

• Miltefosine vs SSG (Ethiopia)
  – HIV-: safe and effective
  – HIV+: safer and but less effective

• L-AmB
  – Dose-finding multi-continent study
    • Brazil > Kenya > India
    • Kenya 10 mg/kg TD
  – Sudan
    • High dose needed for complicated cases (20-30 mg/kg)
    • High treatment failure rate
      • Co-morbidity? Strain-effect?

Ritmeijer et al, CID 2006
Seaman et al, CID 1995; Mueller et al, TRSTMH 2007
Combination therapy in Africa
Planned studies (DNDi):

- AmBisome VL – E. Africa
  - Start Jan 2009
  - L-AmB monotherapy
    - Single dose 7.5 – 15 mg/kg vs standard 21 mg/kg over 21 days (7x3 mg/kg)
  - Registration purposes

- Combination studies (phase II)
  - Start planned in 2009
  - Treatment arms
    - L-AmB 10 mg/kg sd + MF 2.5 mg/kg 10 days
    - L-AmB 10 mg/kg sd + SSG 20 mg/kg 10 days
    - MF 2.5 mg/kg 28 days
Combination therapy: options

• Several trial data becoming available
  – Africa
    • SSG + PM
    • L-AmB + MF
    • L-AmB + SSG
  – Asia
    • L-AmB + MF
    • L-AmB + PM
    • MF + PM

• What can we expect from combination therapy?
• Which factors will determine our choice?
Efficacy and safety

- Minimum efficacy
  - Initial Cure > 95%
  - Definitive Cure > 90% (6 months)
- Special populations/Effectiveness
  - HIV
  - Co-morbid conditions (excluded in RCT)
  - Pregnancy
- Toxicity
Compliance

- MF
  - 28-day treatment (ambulatory) is challenging
    - Phase IV study
      - End of treatment: 95.5%
      - 6 months of FU: 85.6%
  - 7-10 days treatment more feasible
Cost-effectiveness

- Data Filip Meheus
Feasibility and acceptability

- Health infrastructure: Capacity
  - IV/IM treatment
  - Monitoring for ambulatory treatment
    - MF, PM
    - MF: contraception
- Disease burden
- Reliable drug availability (cost)
- Second line options (HIV, relapse)
Resistance

- Limited understanding of dynamics of development and spread of drug resistance
  - Rational design of resistance-prevention strategy?
- Short, well tolerated and effective combination therapy as strategy to prevent resistance
Regional factors

- Resistance pattern
- Strain susceptibility?
  - PM? L-AmB?
- Pharmacokinetics
  - PM?
- Co-morbidity
  - HIV, tuberculosis, malnutrition
- Health systems
Future challenges

- Resistance
  - Most effective way to prevent resistance?
- Regional factors
- Pharmacovigilance
- Complexity
  - Stable delivery of one drug is already challenging