Current and Emerging Approaches in Antileishmanial Research

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Drugs for Neglected Diseases initiative

WorldLeish4, February 3rd, 2009
## Current Treatments

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Pentavalent Antimonials</th>
<th>Amphotericin B</th>
<th>Liposomal Amphotericin B</th>
<th>Miltefosine</th>
<th>Paromomycin sulphate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen</td>
<td>20 mg/kg daily for 20-30 days (depends on geographic area)</td>
<td>1 mg/kg e.o.d. for up to 30 Days (15mg/Kg total dose)</td>
<td>5-20 mg/kg total dose in 4-10 doses over 10-20 days</td>
<td>1.5-2.5 mg daily over 28 days (India only)</td>
<td>15mg/kg/ for 21 days (India only)</td>
</tr>
<tr>
<td>Marketing authorisation holder</td>
<td>Albert David (SSG) GSK (Pentostam) Sanofi Aventis (Glucantime)</td>
<td>Bristol Meyers Squibb (Fungizone) Generic companies</td>
<td>Gilead (AmBisome®)</td>
<td>Paladin (Impavido)</td>
<td>Gland Pharma / IOWH</td>
</tr>
<tr>
<td>Administration</td>
<td>iv or im</td>
<td>iv</td>
<td>Iv</td>
<td>Oral</td>
<td>im</td>
</tr>
<tr>
<td>Clinical efficacy Asia Africa South America</td>
<td>35-95% (depending on geographic area)</td>
<td>&gt; 97% all regions</td>
<td>&gt; 97%; single dose: 91% Not fully established Not fully established</td>
<td>94-97% (India); Not established Not established</td>
<td>94% (India) In evaluation Assumed to be limited</td>
</tr>
<tr>
<td>Resistance</td>
<td>As high as 60% (Bihar, India)</td>
<td>Not documented</td>
<td>Not documented</td>
<td>Lab isolates</td>
<td>Lab isolates</td>
</tr>
<tr>
<td>Toxicity</td>
<td>+++ Cardiac toxicity, pancreatitis, nephrotoxicity hepatotoxicity</td>
<td>+++ Nephrotoxicity (in patient care needed)</td>
<td>+ Some nephrotoxicity</td>
<td>+ Gastro-intestinal (20-55% of patients, usually mild), nephrotoxicity hepatotoxicity Possible teratogenicity</td>
<td>+ Nephrotoxicity ototoxicity hepatotoxicity (all relatively rare)</td>
</tr>
<tr>
<td>Approximate cost of drugs per course* USD (Euros)</td>
<td>SSG (AD) <del>$50 (37€) Glucantime (SA)</del> $70 (52 €) (Based on 30 day course)</td>
<td>Generic price: ~ $117 (87€)</td>
<td>Preferential price: $280 (207€) (for 20mg/kg total dose) Commercial price: ~10x above costs</td>
<td>Preferential price: ~ $74 ( 54 €) (can be obtained at 46€ if buying &gt;75 000 packs) Commercial price: ~ $150</td>
<td>~ $10 (7.3 €)</td>
</tr>
<tr>
<td>Issues</td>
<td>Quality control Availability Length of treatment Painful injection Toxicity Resistance in India</td>
<td>Need for slow iv infusion Dose-limiting nephrotoxicity Heat stability</td>
<td>Price Need for slow iv infusion Heat stability (Stored &lt;25° C)</td>
<td>Price Possible teratogenicity Potential for resistance Patient compliance</td>
<td>Efficacy variable Between and within regions</td>
</tr>
</tbody>
</table>
Issues with Current Treatments

• **SSG/ antimonials:** SAFETY, RESISTANCE, DURATION
  - **Africa:** registered in Sudan, Ethiopia, Kenya. Used for all above indications!
  - **India:** SSG failure in Bihar, still effective other areas

• **AmBisome®:** COST, FEASIBILITY
  - **Africa:** MSF Ethiopia field use, Dose escalation study planned
  - **India:** Phase 2 data+, combo studies done/ planned, MSF- 20mg in field setting (1000+)

• **Ampho B:** SAFETY, DURATION, COST
  - **Africa:** being replaced by Ambisome, limited use
  - **India:** Large scale use especially in private sector in Bihar (SSG failure)

• **Paromomycin:** DURATION, EFFICACY?
  - **Africa:** currently under trial, used as part 1° Rx in S Sudan by MSF
  - **India:** Registered for use, Phase 4 ongoing

• **Miltefosine:** DURATION, SAFETY, COMPLIANCE
  - **Africa:** RCT done Ethiopia, no current trials underway, 2 previously planned (no funding)
  - **India:** Registered in India, WHO roll out, In private sector, In combo studies planned
## VL Target Product Profile

<table>
<thead>
<tr>
<th>Target</th>
<th>Target Label VL and PKDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spp</td>
<td>All species</td>
</tr>
<tr>
<td>Distribution</td>
<td>All areas</td>
</tr>
<tr>
<td>Target Population</td>
<td>Immunocompetent and immunosuppressed</td>
</tr>
<tr>
<td>Clinical Efficacy</td>
<td>&gt; 95%</td>
</tr>
<tr>
<td>Resistance</td>
<td>Active against resistant strains</td>
</tr>
<tr>
<td>Safety and Tolerability</td>
<td>No AEs requiring monitoring</td>
</tr>
<tr>
<td>Contraindications</td>
<td>None</td>
</tr>
<tr>
<td>Interactions</td>
<td>None- Compatible for combination therapy</td>
</tr>
<tr>
<td>Formulation</td>
<td>Oral / im depot</td>
</tr>
<tr>
<td>Stability</td>
<td>3 yrs in zone 4</td>
</tr>
<tr>
<td>Treatment Regimen</td>
<td>1/day for 10 d po/ 3 shots over 10 d</td>
</tr>
<tr>
<td>Cost</td>
<td>&lt; $10 / course ($20 in 7 years)</td>
</tr>
</tbody>
</table>
VL Preclinical and Clinical Portfolio

- **Preclinical Efficacy & Safety**
  - Buparvaquone
  - Oral AmphoB (iCo)
  - Oral AmphoB (BDSI)
  - Miltefosine Africa
  - Sitamaquine & Tafenoquine (GSK)

- **Clinical**
  - AmBisome®
  - PM-SSG Africa

- **Registration**
  - VL Combo Asia
  - PM – India (iOWH)

- **Ph IV**
  - PM – India (iOWH)

- **Combination Trials**
  - Sitamaquine & Tafenoquine (GSK)
  - Oral AmphoB (BDSI)
  - Amphomul (Bahrat)

- **DNDi projects**
- **Non-DNDi projects**
DNDi Near- and Long-Term Strategy

• Ensure appropriate use of existing treatments through clinical validation of combination therapy treatments.

• Develop new formulations of existing drugs (ie. Amphotericin B)

• Identify and develop NCE
DNDi R&D Portfolio - 2009

- Consolidation with strategic focus
  - By chemical structure
  - By target
  - General screening
  - New partners
- Reference Screening Centers
  - LSHTM
  - STI
  - U. Antwerp

HAT
Scynexis

VL
Advinus, CDRI

Chagas
CDCO/ Epichem

New HAT Candidate
Buparvaquone

AmphoB polymer
Oral AmphoB

Fexinidazole (HAT)

VL Combination
In Asia
Paromomycin in E. Africa
AmBisome® in E. Africa
Miltetosine in E. Africa
VL Combination in LA
Paediatric Benznidazole
Azoles (Chagas)

FACT-ASAQ
FACT-ASMQ
NECT

30% 65% 55% 55% 70% 50% 65% 95%

Screen  Lead ID  Lead Optimization  Preclinical Efficacy Safety  Ph I  Ph II  Ph III  Registration  Ph IV & Access
DNDi Early-Stage Discovery

- Forge alliance with group with complementary skill set
  - Multiple targets, broad capabilities, proven record, less management burden (U. Dundee)

- Continue to be opportunistic
  - Phasing out some one-off type of agreements as they mature, consider opportunities as they arise

- Data mining
  - STI, WRAIR

- Fill in gaps in HTS assays
  - Improvements in through-put for *T. cruzi* and *Leishmania* screens (IPK)

- Library access
  - Expand current list - pharma, ad hoc suppliers,
  - Sharing with PDPs
  - Targeted drug classes
DNDi consortium is partially funded by the Bill & Melinda Gates Foundation.
Examples of Active Scaffolds

**Oxaboroles**
- IC\textsubscript{50} 2.03 uM
- IC\textsubscript{50} 2.03 uM
- IC\textsubscript{50} 0.95 uM
- IC\textsubscript{50} 2.69 uM

**2-substituted quinolines**

**Amphotericin B**

**Buparvaquone**
Unique Features of Boron that are Different from Carbon

Boron is normally trivalent and trigonal planar in structure.
It has an empty P-orbital & can form a new bond under specific conditions.

The new bond forms a tetrahedral structure.

Exploiting the P-orbital reactivity allows rational drug design and creation of compounds with unique properties beyond traditional small molecule drugs.
Amphotericin B Formulations

- AmB is the most efficient treatment

- Cost, stability and route of administration are barriers for wider use

- Ongoing work to develop cheaper and orally active formulations
Potential cheaper iv Ampho B formulation

Replace the liposoamal part by polyacrylic acid polymer

**Synthesis of monomer**

1. Acid chloride + NHS → DCM, Et$_3$N → Active ester monomer

2. Controlled radical polymerisation ATRP → Active ester polymer precursor

3. AmB + NaOH → Non-covalent complex → AmB-PMA Complex

**Preparation of AmB complex**

Amphotericin B (AmB)
Summary of Progress

• Complexes have been made with the following features:
  – MW: from 12 kDa to 150 kDa
  – Loading: from 15% to 60%
  – Amphotericin dose: from 0.75 to 1.5 mg

• Complexes can be made directly from the polymer. No need to use the precursor polymer.

• No sign of AmB-related toxicity in mice.

• Issues:
  How the physicochemical properties of the complex correlates to efficacy in the *in vivo* model.
AmB Oral Formulations

• Orally active AmB formulations under development
  
  – Lipid-based formulation developed by iCo pharmaceuticals (pre-clinical stage)

  – "Cochleates" formulation developed by BDSI in collaboration with DNDi
BDSI Cochleates Technology

- Stable, phospholipid-calcium precipitates
- Self-assembling crystalline units
- Multilayered structure, containing little or no internal aqueous space
- Resistant to degradation in GI tract
- Increases processing and shelf-life stability
- Composed of naturally occurring materials
- Very inexpensive cost of goods and manufacturing
iCo Lipid-Based Formulation

• The laboratory of Dr. Kishor Wasan of the University of British Columbia has made significant strides toward the development of a proprietary, lipid-based AmB formulation for oral administration.

• Further development licensed to iCo Therapeutics and collaboration with CPDD.
Conclusions

• No new treatments recently made available to treat leishmaniasis

• Limited number of promising chemical series available

• International consortium built around Indian partners with international collaborations
Teams

Advinus Team (Management)
Koushik Das Sharma
Vadiraj Gopinath
Vikram Ramanathan
Sanjiban Banerjee

Advinus Team (Scientists)
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Manjunath Moger
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Sabath Kumar P
Venkatesan Jayakumar S
Srinivas Rao P
Saswati Roy
Shubhangi Bhosale
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