Drug combinations against soil-transmitted helminths

Swiss TPH Winter Symposium 2017
Helminth Infection – from Transmission to Control

Basel, 7 December 2017
Cure and egg reduction rates of recommended drugs (single dose) for soil-transmitted helminthiasis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cure Rate</th>
<th>Egg Reduction Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mebendazole</td>
<td>96.2</td>
<td>42.1</td>
</tr>
<tr>
<td>Albendazole</td>
<td>95.7</td>
<td>30.7</td>
</tr>
<tr>
<td>Pyrantel pamoate</td>
<td>92.6</td>
<td>20.2</td>
</tr>
<tr>
<td>Levamisole</td>
<td>97.3</td>
<td>29.5</td>
</tr>
</tbody>
</table>

Efficacy of Current Drugs Against Soil-Transmitted Helminth Infections
Systematic Review and Meta-analysis

Jennifer Keiser, PhD
Jürg Utzinger, PhD

Context: More than a quarter of the human population is likely infected with soil-transmitted helminths (Ascaris lumbricoides, hookworm, and Trichuris trichiura) in highly endemic areas. Preventive chemotherapy is the mainstay of control, but only 4 drugs...
Cure rate *T. trichiura* 1995 versus 2015

<table>
<thead>
<tr>
<th></th>
<th>1995</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albendazole</td>
<td>38.6</td>
<td>16.4</td>
</tr>
<tr>
<td>Mebendazole</td>
<td>47.5</td>
<td>29.2</td>
</tr>
</tbody>
</table>

Significantly reduced efficacy → Resistance development?

→ Need for new anthelminthic treatments
New/alternative drugs

• Tribendimidine
  • Broad spectrum of activity (nematodes and trematodes)
  • High activity against liver flukes
  • High activity against hookworm; else, similar to albendazole
  • FDA registration ongoing

• Oxantel pamoate
  • Excellent trichuricidal drug, no longer marketed

• Ivermectin
  • On the essential medicine list
  • Activity against filarial infections, *A. lumbricoides* and *S. stercoralis*

• Moxidectin
  • FDA registration ongoing for onchocerciasis
  • Activity against *S. stercoralis*
Drug combinations

• None of the recommended/alternative drugs covers all soil-transmitted helminth species with acceptable efficacy at a single dose → broaden the spectrum of efficacy

• Treating simultaneously with 2 drugs from different anthelmintic classes (e.g. benzimidazoles, macrocyclic lactones) → slow development/ prevent drug resistance

• Increased efficacy? Not known whether drug combinations exhibit → synergistic effects
Drug combination tiers

Expert meeting in Seattle (March 2016) identified priority combinations based on available evidence

**Tier 1**: albendazole + ivermectin

**Tier 2**: albendazole + oxantel (or oxantel/pyrantel)

**Tier 3**: tribendimidine and moxidectin combinations

**Tier 4**: novel treatments, e.g. emodepside plus partner drug
Tier 1: Albendazole-ivermectin

- BMGF grant (“Optimizing Drug Therapy against Soil-Transmitted Helminthiasis”) since 11/2016
- Combination included in Essential Medicine List for treatment of soil-transmitted helminthiasis early 2017
- Meta-analysis on efficacy and safety, analysis of individual patient data:
  - 466 studies screened, 4 studies identified

<table>
<thead>
<tr>
<th>Study</th>
<th>IVM + ALB</th>
<th>ALB alone</th>
<th>IVM alone</th>
<th>Studied parasites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belizario et al., 2003</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>T. trichiura, A. lumbricoides</td>
</tr>
<tr>
<td>Speich et al., 2015</td>
<td>X</td>
<td></td>
<td></td>
<td>T. trichiura, A. lumbricoides, hookworm</td>
</tr>
<tr>
<td>Knopp et al., 2010</td>
<td>X</td>
<td></td>
<td></td>
<td>T. trichiura, A. lumbricoides, hookworm</td>
</tr>
<tr>
<td>Ismail et al., 1999</td>
<td>X</td>
<td></td>
<td></td>
<td>T. trichiura</td>
</tr>
</tbody>
</table>
Albendazole-ivermectin *versus* albendazole *T. trichiura*

<table>
<thead>
<tr>
<th>Study</th>
<th>Favors IVM + ALB</th>
<th>Weight</th>
<th>Relative Risk [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belizario <em>et al.</em> 2003</td>
<td></td>
<td>37.63%</td>
<td>0.51 [0.40, 0.65]</td>
</tr>
<tr>
<td>Ismail <em>et al.</em> 1999</td>
<td></td>
<td>19.52%</td>
<td>0.33 [0.18, 0.61]</td>
</tr>
<tr>
<td>Knopp <em>et al.</em> 2010</td>
<td></td>
<td>42.85%</td>
<td>0.69 [0.60, 0.79]</td>
</tr>
</tbody>
</table>

**Model-based estimate of RR:**

Random Effects Model

0.53 [0.38, 0.76]

Albendazole-ivermectin significantly reduces the risk of still being infected after treatment.
Egg reduction rates in *T. trichiura* patients

Egg reduction rates (%)

Individual ERRs (%)
No greater benefit against hookworm and *A. lumbricoides*

**T. trichiura**

- Knopp
- Belizario
- Ismail

**A. lumbricoides**

- CR of IVM + ALB
- CR of IVM alone
- CR of ALB alone

**Hookworm**

- CR of IVM + ALB
- CR of IVM alone
- CR of ALB alone
Tier 1: Albendazole-ivermectin

- Multi-country/continent study planned:
- Evaluation of safety and efficacy of albendazole-ivermectin versus albendazole in Tanzania, Laos and Côte d’Ivoire
- Sample size: n=600 (300 per arm) per site
- One baseline and three follow-up assessments at day 21, day 180, and day 360
- Retreatment on day 180 of positive participants according to their trial allocation
Clinical studies
Evaluation of 2 stool samples pre- and post-treatment (21 days) using the Kato-Katz method for the determination of cure and egg reduction rates
Clinical examination and treatment
Tier 2: Albendazole-oxantel pamoate

- Evidence from 4 studies (2012-2016)

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Cure rates (95%CI)</th>
<th>Egg reduction rates (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>A. lumbricoides</em></td>
<td>312</td>
<td>95.5 (84.9-98.8)</td>
<td>98.9 (91.6-100.0)</td>
</tr>
<tr>
<td>Hookworm</td>
<td>395</td>
<td>66.1 (38.6-85.6)</td>
<td>85.7 (68.7-100.0)</td>
</tr>
<tr>
<td><em>T. trichiura</em></td>
<td>519</td>
<td>75.0 (44.8-91.7)</td>
<td>93.6 (79.3-100.0)</td>
</tr>
</tbody>
</table>

- Oxantel pamoate can be administered by weight independent dose (500 mg)
Tier 3: Tribendimidine combinations

Randomized trial on Pemba and in Côte d’Ivoire in 2016

- Tribendimidine plus ivermectin
- Tribendimidine plus oxantel pamoate
- Albendazole plus oxantel pamoate
- Tribendimidine plus placebo

Primary outcome: egg reduction rate against hookworm, assessed for non-inferiority (3% margin)

Secondary outcomes: safety, efficacy against *T. trichiura* and *A. lumbricoides*

Sample size: 640 adolescents aged 15-20 years (n=400 Pemba, 240 Côte d’Ivoire; 160 per treatment arm)
Results: Efficacy

Hookworm

TRB-IVER vs. ALB-OXP
99.5% vs. 96.0%
Difference 3.52 (2.05 to 5.65)

TRB-OXP vs. ALB-OXP
96.5% vs. 96.0%
Difference 0.48 (-1.61 to 2.88)
Results: Adverse events

- Pre-treatment
- 3 hours post-treatment
- 24 hours post-treatment

Efficacy and safety of tribendimidine, tribendimidine plus ivermectin, tribendimidine plus oxantel pamoate, and albendazole plus oxantel pamoate against hookworm and concomitant soil-transmitted helminth infections in Tanzania and Côte d’Ivoire: a randomised, controlled, single-blinded, non-inferiority trial

Wendelin Muser, Jean T. Cuckorley, Said M. Ally, Shadil H. Jere, Aumaar K. Ansum, Richard E. Yapi, Marco Albanico, Maxine Pushkar, Jorg Horzeller, Jan Hetterolf, Jorn Korin
Tier 3: Moxidectin combinations

- Randomized controlled trial on Pemba, Tanzania in 2017

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albendazole (400 mg)</td>
<td>Oxantel pamoate (25 mg/kg)</td>
</tr>
<tr>
<td>Moxidectin (8 mg)</td>
<td>Placebo</td>
</tr>
<tr>
<td>Moxidectin (8 mg)</td>
<td>Albendazole (400 mg)</td>
</tr>
<tr>
<td>Moxidectin (8 mg)</td>
<td>Tribendimidine (400 mg)</td>
</tr>
</tbody>
</table>

- Moxidectin-albendazole not inferior to albendazole-oxantel (egg reduction rate against *T. trichiura*)
- Moxidectin-albendazole *versus* moxidectin
- Moxidectin-albendazole *versus* moxidectin-tribendimidine
- Sample size: 640 adolescents aged 15-20 years
Results: Adverse events

- Constipation
- Cough
- Headache
- Nausea
- Vomiting
- Diarrhea
- Stomachache
- Itching
- Fever
- Dizziness
- Thrill

Percentage (%)

3h post treatment 24h post treatment 48h post treatment

- Moxidectin
- Moxidectin/Tribendimidine
- Moxidectin/Albendazole
- Albendazole/Oxantel pamoate
Tier 4: Novel drugs--emodepside

- Veterinary anthelminthic used in dogs and cats
- Development by DNDi for the treatment of onchocerciasis ongoing
- Hookworm and whipworm *in vitro* and *in vivo* models at Swiss TPH
- High activity against *T. muris* in vivo: ED$_{50}$ of 2.25 mg/kg
- High activity against *N. americanus* in vivo: ED$_{50}$ of 1.4 mg/kg
- *A. ceylanicum* evaluation ongoing

A. ceylanicum L3

T. muris L1
Conclusion

• Drug combinations are the way forward for the treatment of soil-transmitted helminthiases
• Generated a large body of evidence on the efficacy of different drug combinations
• Oxantel pamoate combinations reveal highest efficacy against *T. trichiura* infections followed by ivermectin or moxidectin combinations
• Tribendimidine has high efficacy against hookworm, particular in combination with ivermectin and moxidectin (synergism?)
• Triple dose therapy pyrantel-oxantel pamoate-albendazole significant higher activity than co-administrations with 2 drugs
• Availability of drugs need to be secured
• Emodepside might be a promising alternative anthelminthic drug alone or in combination
Acknowledgements

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