Controlled Human Malaria Infection Trials (CHMI)

FDA Public Workshop—Clinical Trial Design Considerations for Malaria Drug Development

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CHMI Support of Product Development

Target Product Profiles
- Preventive
- Therapeutic

Method of infection
- Infected mosquito
- Direct Venous Inoculation

Method of diagnosis
- Nucleic acid tests
- Rapid diagnostics
- Thick blood smear

Method of product administration
- Dose (de)-escalation
- Time-shift
- Vaccine via IV, IM, ID, regimen optimization

Opportunities for discovery
- Protective phenotypes
- Antigen selection
Target Product Profile

Preventive
• Pregnant women and children in endemic settings
• Travelers
• Military
• Post exposure prophylaxis
• Repeat exposures

Therapeutic
• Plasmodia species
• Control of severe disease
• Control of further transmission
• In combination with other drugs
• Concurrent infections
Human Malaria Infection

Caused by a parasite *Plasmodium*

Five *Plasmodium* species:
- *P. falciparum*
- *P. vivax*
- *P. ovale*
- *P. malariae*
- *P. knowlesi*
- *P. brasillianum*

Complex life cycle with many parasite forms and stages.

Transmitted by mosquito. Only mosquitoes can spread the parasite to another human.

Malaria is not infectious from person to person. You cannot give malaria to someone else.
The Nobel Prize in Physiology or Medicine 1902
Ronald Ross

"for his work on malaria, by which he has shown how it enters the organism and thereby has laid the foundation for successful research on this disease and methods of combating it".
The Nobel Prize in Physiology or Medicine 1927
Julius Wagner-Jauregg

"for his discovery of the therapeutic value of malaria inoculation in the treatment of dementia paralytica"

This discovery led to the testing of patients for syphilis at the former London Asylum that same year using the Wassermann test. In 1921, of 1131 patients tested, slightly over 10% were discovered to have syphilis. The malarial treatment of neurosyphilis was widespread by the 1930s, and continued to be used until the introduction of penicillin in the 1940s.
Fig. 1 Year cohorts versus frequency for types of treatment used at the Boston City Hospital.

Diana Patterson, Joel A. Vilensky, Wendy M. Robertson, Joseph Berger

Treatment and diagnostic accuracy of neurosyphilis at Boston City Hospital’s Neurological Unit, 1930–1979

Journal of the Neurological Sciences, Volume 314, Issues 1–2, 2012, 1 - 4
What is CHMI?

Controlled human malaria infection (CHMI) is now used to test vaccines and drugs, as well as to examine physiological and immunological responses to malaria parasites.

- Sporozoite-induced malaria infection (SIM)
  - Via direct venous inoculation
  - Via infected anopheles bites
- Induced blood stage malaria infection (IBSM)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SIM</th>
<th>IBSM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PfSPZ Challenge</td>
<td>Anopheles</td>
</tr>
<tr>
<td>Safety record</td>
<td>3400</td>
<td>&gt;1500</td>
</tr>
<tr>
<td>Risk of introduction of adventitious agents</td>
<td>Minimal</td>
<td>Minimal</td>
</tr>
<tr>
<td>Ability to vary size of inoculum</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Knowledge of size of inoculum</td>
<td>+++</td>
<td>+/-</td>
</tr>
<tr>
<td>Logistical ease</td>
<td>LN2, transport, DVI</td>
<td>Need for insectary</td>
</tr>
<tr>
<td>Availability</td>
<td>Sanaria</td>
<td>Widespread</td>
</tr>
<tr>
<td>Life cycle stages amenable to study</td>
<td>All human stages</td>
<td>All human stages</td>
</tr>
</tbody>
</table>

### Methods of Sporozoite-Induced Malaria Infection

<table>
<thead>
<tr>
<th>Pf Infected Mosquito bite</th>
<th>Pf SPZ via Direct Venous Inoculation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pro</strong></td>
<td><strong>Pro</strong></td>
</tr>
<tr>
<td>Natural route</td>
<td>Easier implementation</td>
</tr>
<tr>
<td>The ‘gold standard’</td>
<td>Lower cost</td>
</tr>
<tr>
<td>Contains the dermal</td>
<td>More consistent infectious</td>
</tr>
<tr>
<td>interactions between</td>
<td>dose?</td>
</tr>
<tr>
<td>parasite and people</td>
<td>Can achieve same pre-patent period</td>
</tr>
<tr>
<td></td>
<td>as mosquito bite CHMI</td>
</tr>
<tr>
<td><strong>Con</strong></td>
<td><strong>Con</strong></td>
</tr>
<tr>
<td>More expensive</td>
<td>No insectary needed</td>
</tr>
<tr>
<td>Local reactogenicity</td>
<td></td>
</tr>
<tr>
<td>Implementation challenges</td>
<td></td>
</tr>
<tr>
<td>Requires a BSL2 insectary</td>
<td></td>
</tr>
<tr>
<td>Variation in biting</td>
<td></td>
</tr>
<tr>
<td>behavior</td>
<td></td>
</tr>
<tr>
<td>May differ when applied</td>
<td></td>
</tr>
<tr>
<td>to persons from endemic</td>
<td></td>
</tr>
<tr>
<td>regions</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Mosquito Infection

Mosquito cups enter challenge room through pass through

Mosquitoes returned to CeMPMIR post feeding

• Assessed for:
  • Presence of bloodmeal
  • Dissected and assessed for sporozoites
  • Rated using standard 0, 1+, 2+, 3+, 4+ rating

Results recorded on challenge form

Repeat until 5 infected bites at ≥2+ rating achieved
# Malaria Challenge

<table>
<thead>
<tr>
<th>Salivary gland score</th>
<th>Approximate number of sporozoites</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>no sporozoites observed</td>
</tr>
<tr>
<td>+1</td>
<td>1-10 sporozoites observed</td>
</tr>
<tr>
<td>+2</td>
<td>11-100 sporozoites observed</td>
</tr>
<tr>
<td>+3</td>
<td>101-1000 sporozoites observed</td>
</tr>
<tr>
<td>+4</td>
<td>&gt;1000 sporozoites observed</td>
</tr>
</tbody>
</table>
Mosquito Challenge SIM Kinetics

Malaria Challenge via DVI

- Thaw of PfSPZ from LN2 and dilution in PBS
- Direct venous inoculation via tuberculin syringe
PfSPZ Challenge SIM Kinetics

All are Pf Mos except:

- D: DVI PfSPZ
- H: ID PfSPZ
- J: ID PfSPZ
- P: IM PfSPZ
CHMI va IBSM

Evaluation of the parasitaemia of the P. falciparum red blood cell banks
- 78%
- 1.5 – 4.5% rings

Confirmation of the identity

Evaluation of the viability
- P. falciparum 7G8 – 15%
- P. falciparum NF54 – 50%

Mycoplasma, endotoxin and viral testing

Identity testing

In vitro anti-malaria drug susceptibility

Quality review
Schematic diagram of the course of induced blood stage malaria infection in human volunteers. Parasite counts are typically measured by qPCR following in vivo inoculation with ~1800 infected red cells containing viable ring stage parasites.
# Methods of Malaria Diagnosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RDT</th>
<th>Thin BS</th>
<th>Thick BS</th>
<th>LAMP</th>
<th>PCR</th>
<th>RT-PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>LoD (1000s para/µL)</td>
<td>100+</td>
<td>100+</td>
<td>5-10</td>
<td>1</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Volume (µL)</td>
<td>30-50</td>
<td>1-2</td>
<td>5</td>
<td>30</td>
<td>500</td>
<td>50</td>
</tr>
<tr>
<td>Turnaround time (hr)</td>
<td>&lt;0.5</td>
<td>&lt;1</td>
<td>&lt;12</td>
<td>1-2</td>
<td>6-24</td>
<td>6-24</td>
</tr>
<tr>
<td>High-throughput</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Point-of-care</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Internal control</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Useful* pooling</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Species ID</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+**</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Gametocytes</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>‘One-tube’ multiplex</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cost</td>
<td>$$</td>
<td>$</td>
<td>$</td>
<td>$-$$</td>
<td>$$$</td>
<td>$$$</td>
</tr>
</tbody>
</table>

LoD, limit of detection; *LoD < 1 parasite/µL; **Requires multiple tubes
Diagnosis vs. Clinical Symptoms

Prepatent Period (days)
- Mean: 11.2
- Median: 11.0
- Range: 9-14

Incubation Period (days)
- Mean: 9.7
- Median: 9.5
- Range: 6-14

Onset of symptoms
- Prior to 1st + BS: 3 (50%)
- Day of 1st + BS: 2 (33.3%)
- After 1st + BS: 1 (16.7%)
Product Administration vis a vis CHMI

Preventive/prophylaxis studies
- Time-shift of single administration at a fixed dose prior to CHMI
  - Provides more precision for PK/PD
- Dose de-escalation at a fixed time (or narrow window) prior to CHMI
  - Very informative for further development
- Multiple dose, multiple CHMI
  - Representative of the field

Therapeutic studies
- Dose escalation/de-escalation
- Diagnostic threshold
- Timing of rescue therapy
- Intermittent presumptive therapy
- Combination therapy
- Impact of coinfection on antimicrobial chemotherapy and drug resistance
Method of Product Administration

Drugs – Pharmacokinetics

Liberation - release

Absorption - entering the blood circulation.

Distribution - dispersion throughout the body.

Metabolization (or biotransformation, or inactivation) – transformation of parent compounds into daughter metabolites.

Excretion
CHMI vis SIM (Dx with NAT)
CHMI vis SIM (Dx with TBS)
Nested Nomenclature

A correlate of protection (CoP) may either be a mechanism of protection, termed mCoP, or a non-mechanism of protection, termed nCoP, which predicts vaccine efficacy through its (partial) correlation with another immune response(s) that mechanistically protects. From Plotkin and Gilbert (2008)
Opportunities for Discovery

- Controlled Human Malaria Infection (CHMI)
- Sporozoite Induced Malaria (SIM)
- Induced Blood Stage Malaria (IBSM)
Acknowledgments

Study Participants

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THANK YOU

seattlemalaria.org