Translational tools for Early Development of Antimalarials: The Human Malaria Challenge Model

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Outline

• The context of antimalarial drug development
  • The Target Product Profile
  • The existential threat of artemisinin resistance
  • Impediments to efficacy testing candidate antimalarials in humans
• How do the human challenge models help development of new antimalarial drugs (& vaccines)
  • Study endpoints
  • Collection of key data for pharmacometric analysis
• Future prospects
New developments in anti-malarial target candidate and product profiles

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Abstract
A decade of discovery and development of new anti-malarial medicines has led to a renewed focus on malaria elimination and eradication. Changes in the way new anti-malarial drugs are discovered and developed have led to a dramatic increase in the number and diversity of new molecules presently in preclinical and early clinical development. The twin challenges faced can be summarized by multi-drug resistant malaria from the Greater Mekong Sub-region, and the need to provide simplified medicines. This review lists changes in anti-malarial target candidate and target product profiles over the last 4 years. As well as new medicines to treat disease and prevent transmission, there has been increased focus on the longer term goal of finding new medicines for chemoprevention, potentially with long-acting molecules, or parenteral formulations. Other gaps in the malaria armamentarium, such as drugs to treat severe malaria and endectocides (that kill mosquitoes which feed on people who have taken the drug), are defined here. Ultimately the elimination of malaria requires medicines that are safe and well-tolerated to be used in vulnerable populations: in pregnancy, especially the first trimester, and in those suffering from malnutrition or co-infection with other pathogens. These updates reflect the maturing of an understanding of the key challenges in producing the next generation of medicines to control, eliminate and ultimately eradicate malaria.

Keywords: Malaria, Plasmodium, Elimination drug discovery, Eradication drug discovery, Medicines, Target candidate profile, Target product profile.

TCP1 Case management of uncomplicated malaria
TCP1 Case management of severe malaria
TCP3 Case management of relapsing malaria
TCP4 Chemoprotection
TCP5 gametocides
TCP6 endectocides
Chemoprevention of vulnerable populations

Burrows et al. Malaria J. 2017
Complex considerations in the development of new antimalarials

• Only co-formulations will be developed
  • Matched or mismatched PK profiles?
  • Drug activity
    • Fast + slow killer?
    • Synergy/Antagonism
  • Selection of resistance
  • Interacting toxicology issues

• Pediatric and pregnant target population
Spread of multidrug resistant malaria parasites in the Greater Mekong Subregion

Figure 4 Normalized *P. falciparum* parasite clearance curves showing the fraction of initial parasitemia versus time in patients treated with artesunate in Western Cambodia and Western Thailand. Parasite clearance was significantly slower in Western Cambodia.

Dondorp et al. (2009) NEJM 361: 456-67

Spread of parasites resistant to both components of Artemisinin Combination Therapy


Difficulties in executing efficacy studies of new antimalarials: Remoteness of potential Phase II trial sites

“We often have to contend with difficult terrain, muddy roads, harsh weather, difficulty communicating with local villagers who have little knowledge of malaria and scarcity of food. The risk of being kidnapped by local bandits is another challenge that we have to face when travelling on a long mobile-team mission to remote villages,” explains Dr Han Min Htet Aung from MAM's malaria project of Yebyu Township.
Finding the right combination from the Global Portfolio of Antimalarials under development

**Product development**

**Preclinical**
- SAR121: Sanofi
- MMV253: Zydus Cadila
- AN13762: SC83288 Heidelberg University
- UCT943: H3D Cape Town
- NPC11618: Mississippi
- MK4815: Merck
- MMV048: (UCT)

**Human volunteers**
- P218: Janssen (Biotec Thailand)
- SJ733: Kentucky/Eisai
- ACT-451840: Actelion
- CDRI 9778: Ipca
- N-tert butyl Isoquine: LSTM/Liverpool/GSK
- M5717: Merck KGaA

**Patient exploratory**
- Cipargamin: Novartis
- DSM265: Takeda (UTSW)
- SAR97276: Sanofi
- Artemisone: UHKST
- AQ13: Immtech
- Sevuparin: Dilaforette
- MMV048 (UCT)

**Patient exploratory in combination**
- Artefenomel/ Ferroroquine: Sanofi
- KAF156/Lumefantrine: Novartis
- Dihydroartemisinin- piperaquine dispersible: Alfasigma/Pierre Fabre
- Artemisinin- pyrimethamine dispersible: Kunming Pharma Co

**Patient confirmatory**
- Tafenoquine: DSM/UTSW, US Army
- Co-trimoxazole: Dilaforette
- Artemether sub-lingual spray: MRC/Suda
- Sulfadoxine- pyrimethamine+ Amodiaquine dispersible: S Kant

**Regulatory review**
- Arteoleone- piperaquine: Sun Pharma
- Rectal artesunate: Strides

**How many combinations to test?**

- \( n! / (k!(n-k)! \)
- Combination of two drugs: \( n \times (n-1)/2 \)
- If \( n=8 \): 29 combinations possible
Improved Murine Model of Malaria Using *Plasmodium falciparum* Competent Strains and Non-Myelodepleted NOD-scid IL2Rγ<sup>−/−</sup> Mice Engrafted with Human Erythrocytes

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Murine models of *Plasmodium falciparum* malaria may become crucial tools in drug discovery. Here we show that non-myelodepleted NOD-scid IL2Rγ<sup>−/−</sup> mice engrafted with human erythrocytes support an infectious burden up to tenfold higher than that supported by engrafted NOD-scid IL2Rγ<sup>−/−</sup> mice. The new model was validated for drug discovery and was used to assess the therapeutic efficacy of 4-pyridones, selective inhibitors of *P. falciparum* cytochrome b<sub>5</sub>.
Experimental human malaria infection: how?

“Natural method”:
- Infected mosquitoes
- Cryopreserved sporozoites

Induced Blood Stage Malaria
### Clinical trial design

| Test drug          | Day | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 |
|--------------------|-----|---|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Outpatient         |     | x | x | x | x | x | x | x | + | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Confinement        |     |   |   |   |   |   |   |   |   |   |   | Q-Pharm |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Drug Rx            |     |   |   |   |   |   |   |   |   |   |   |   | Rescue Drug Treatment as needed |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| PCR (parasites)    |     | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| PCR (gametocytes)  |     | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Mosquito transmission |   | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |

**Parasite Inoculation**

- Clearance of parasitemia over 48-96 hrs
- n=347 subjects
Use of malaria challenge for testing of vaccine efficacy

Payne et al JID 2016
Drug Rx

- Lag Phase
- Parasite Clearance
- Tail Phase

Parasites/ml vs Drug concentration (ng/mL)

Day

MIC
Drugs tested in this system

**Published Studies**
- Artemether/lumefantrine
- Sulfadoxine/pyrimethamine
- Mefloquine
- Ferroquine
- Piperaquine
- ACT-451840
- Griseofulvin
- OZ439 (Artefenomel)
- DSM265

**Unpublished Studies**
- KAE609 (Cipargamin)
- MMV048
- SJ733
- Tafenoquine
- M5717
Does data from human challenge outcome of clinical trials in malaria Patients?

- Defined dose response
- Linking of PD backwards to SCID model and forwards to published Phase II data
Efficacy of OZ439 (artefenomel) against early *Plasmodium falciparum* blood-stage malaria infection in healthy volunteers

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**Objectives:** OZ439, or artefenomel, is an investigational synthetic aziridine antimalarial with similar potency, but a significantly improved pharmacokinetic profile, compared with artemisinins. We wished to measure key pharmacokinetic and pharmacodynamic parameters and the pharmacokinetic/pharmacodynamic relationship of artefenomel in humans to guide the drug’s further development as combination therapy in patients.

**Patients and methods:** We tested artefenomel in the human induced blood-stage malaria (IBSM) model. *Plasmodium falciparum* infection was monitored by quantitative PCR (qPCR) and upon reaching 1000 parasites/ml single doses of 100, 200 and 500 mg of artefenomel were administered orally with evaluation of drug exposure and parasite clearance until rescue treatment after 16 days or earlier, if required.

**Results:** A single 100 mg dose had only a transient effect, while the 200 mg dose resulted in a significant reduction in parasitaemia before early recrudescence. At the highest (500 mg) dose, initial clearance of parasites below the limit of detection of qPCR was observed, with a 48 h parasite reduction ratio (PRR48) >10000 and a parasite clearance half-life of 3.6 h (95% CI 3.4 – 3.8 h). However, at this dose, recrudescence was seen in four of eight subjects 6 – 10 days after treatment. Pharmacokinetic/pharmacodynamic modelling predicted an MIC of 4.1 ng/mL.

**Conclusions:** These results confirm the antimalarial potential of artefenomel for use in a single-exposure combination therapy. The observations from this study support and will assist further clinical development of artefenomel.


- Single dose 100, 200 and 500 mg
- Follow up to SD16
- At 500 mg:
  - PRR$_{48}$ >4
  - Parasite clearance $t_{1/2}$ 3.6 hr
  - MIC: 4.1 ng/ml
A Phase II pilot trial to evaluate safety and efficacy of ferroquine against early Plasmodium falciparum in an induced blood-stage malaria infection study

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Abstract

Background: Ferroquine (SSR97193) is a candidate anti-malarial currently undergoing clinical trials for malaria. To better understand its pharmacokinetic (PK) and pharmacodynamic (PD) parameters the compound was tested in the experimentally induced blood stage malaria infection model in volunteers.

Methods: Male and non-pregnant female aged 18–50 years were screened for this phase II, controlled, single-centre clinical trial. Subjects were inoculated with ~1800 viable Plasmodium falciparum 3D7A-infected human erythrocytes, and treated with a single-dose of 800 mg ferroquine. Blood samples were taken at defined time-points to measure PK and PD parameters. The blood concentration of ferroquine and its active metabolite, SSR97213, were measured on dry blood spot samples by ultra-performance liquid chromatography with tandem mass spectrometry (LC-MS/MS). Parasitaemia and emergence of gametocytes were monitored by quantitative PCR. Safety was determined by recording adverse events and monitoring clinical laboratory assessments during the course of the study.

Results: Eight subjects were enrolled into the study, inoculated with infected erythrocytes and treated with 800 mg ferroquine. Ferroquine was rapidly absorbed with maximal exposure after 4–8 and 4–12 h exposure for SSR97213. Non-compartmental PK analysis resulted in estimates for half-lives of 10.9 and 23.8 days for ferroquine and SSR97213, respectively. Parasite clearance as reported by parasite reduction ratio was 162.9 (95 % CI 141–188) corresponding to a parasite clearance half-life of 6.5 h (95 % CI: 6.4–6.7 h). PK/PD modelling resulted in a predicted minimal parasitoidal concentration of 20 ng/ml, and the single dosing tested in this study was predicted to maintain an exposure above this threshold for 454 h (37.8 days). Although ferroquine was overall well tolerated, transient elevated transaminase levels were observed in three subjects. Paracetamol was the only concomitant treatment among the two out of these three subjects that may have played a role in the elevated transaminases levels. No clinically significant ECG abnormalities were observed.

Conclusions: The parameters and PK/PD model derived from this study pave the way to the further rational development of ferroquine as an anti-malarial partner drug. The safety of ferroquine has to be further explored in controlled human trials.

† Evaluate the Efficacy of a Single Dose Regimen of Ferroquine and Artefenomel in Adults and Children With Uncomplicated P. falciparum Malaria
ClinicalTrials.gov: NCT02497612
Challenge studies to investigate antimalarial activity in the liver
Conclusions

• SCID Mouse and human challenge models provide useful platforms to gain key efficacy data on investigational antimalarials
• They provide key data for pharmacometric analysis

Future Prospects

• Adapt the models to test combinations of antimalarials
• Other lifecycle stages (eg transmission blocking)
• New parasite strains and species (Drug-resistant parasites, *P. vivax*)
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The volunteers