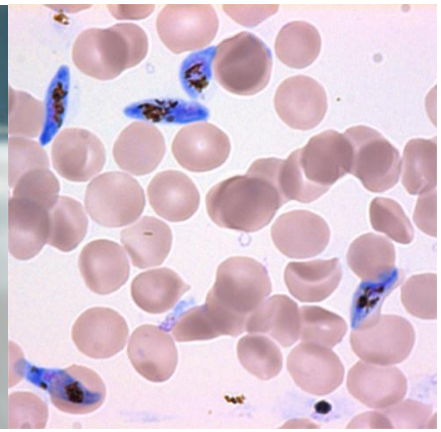
Experience with safety in Controlled Human Malaria Infections

Jona Walk

IABS – 2nd Human Challenge Trials Conference





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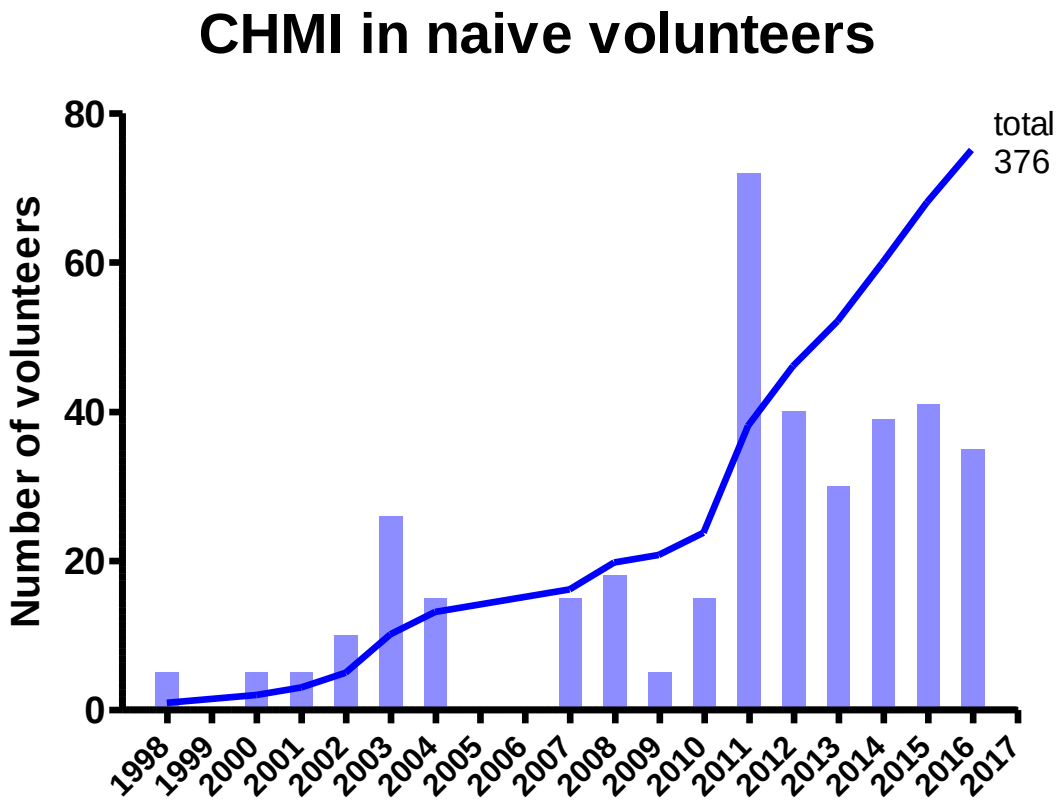
Controlled Human Malaria Infections

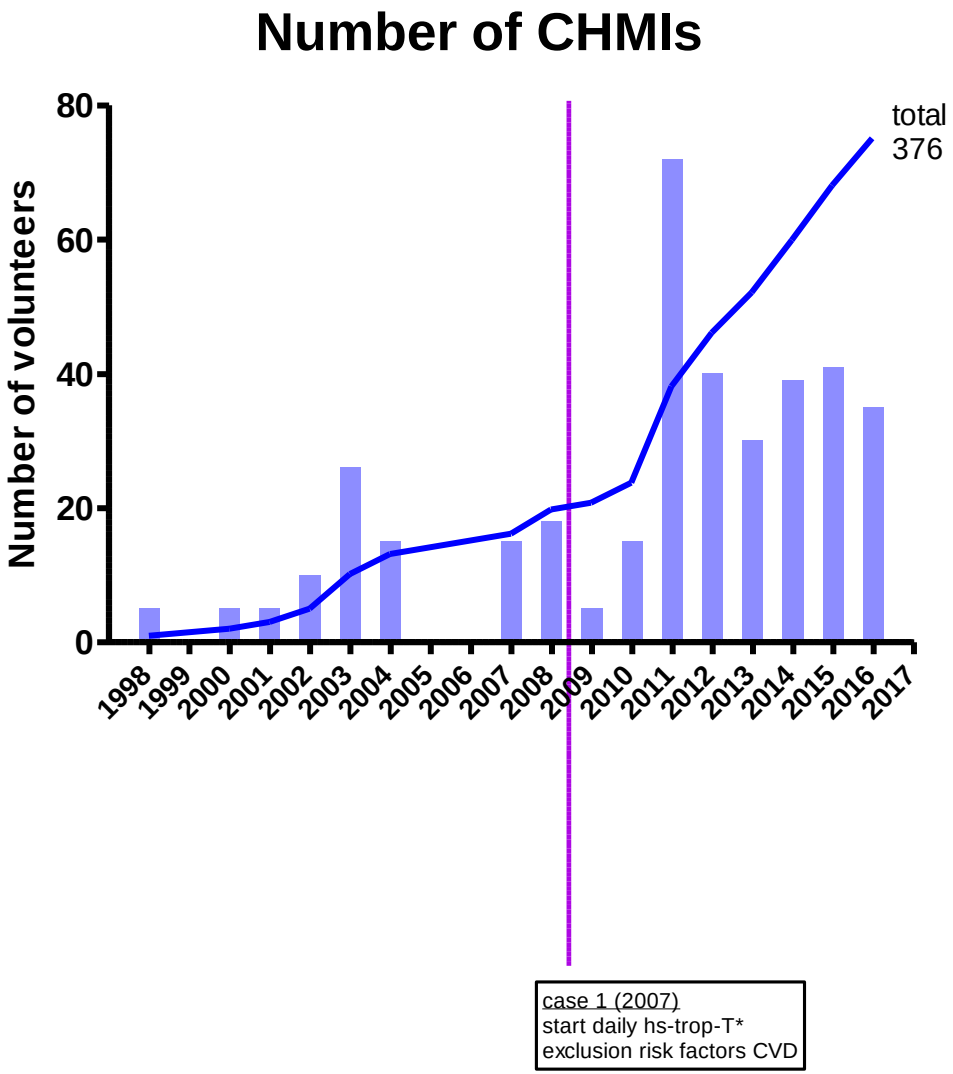


1998 – 2016

- 744 CHMIs
- 376 volunteers

Cardiac events in CHMI

Cardiac events in CHMI



Case 1: Female, 20yrs

- CHMI + artemether/lumefantrine treatment
- Day 16 post CHMI
  - chest pain
  - increased troponin-I
  - ECG abnormalities
- Diagnosis: cardiac event with minimal cardiac damage

Response

- Unexpected adverse event (not known in uncomplicated malaria)
- Expert committee
- CHMI studies on hold
- IRB: How can you ensure safety?
- Start daily troponin-T measurements & other safety labs
- Exclude family history cardiac disease

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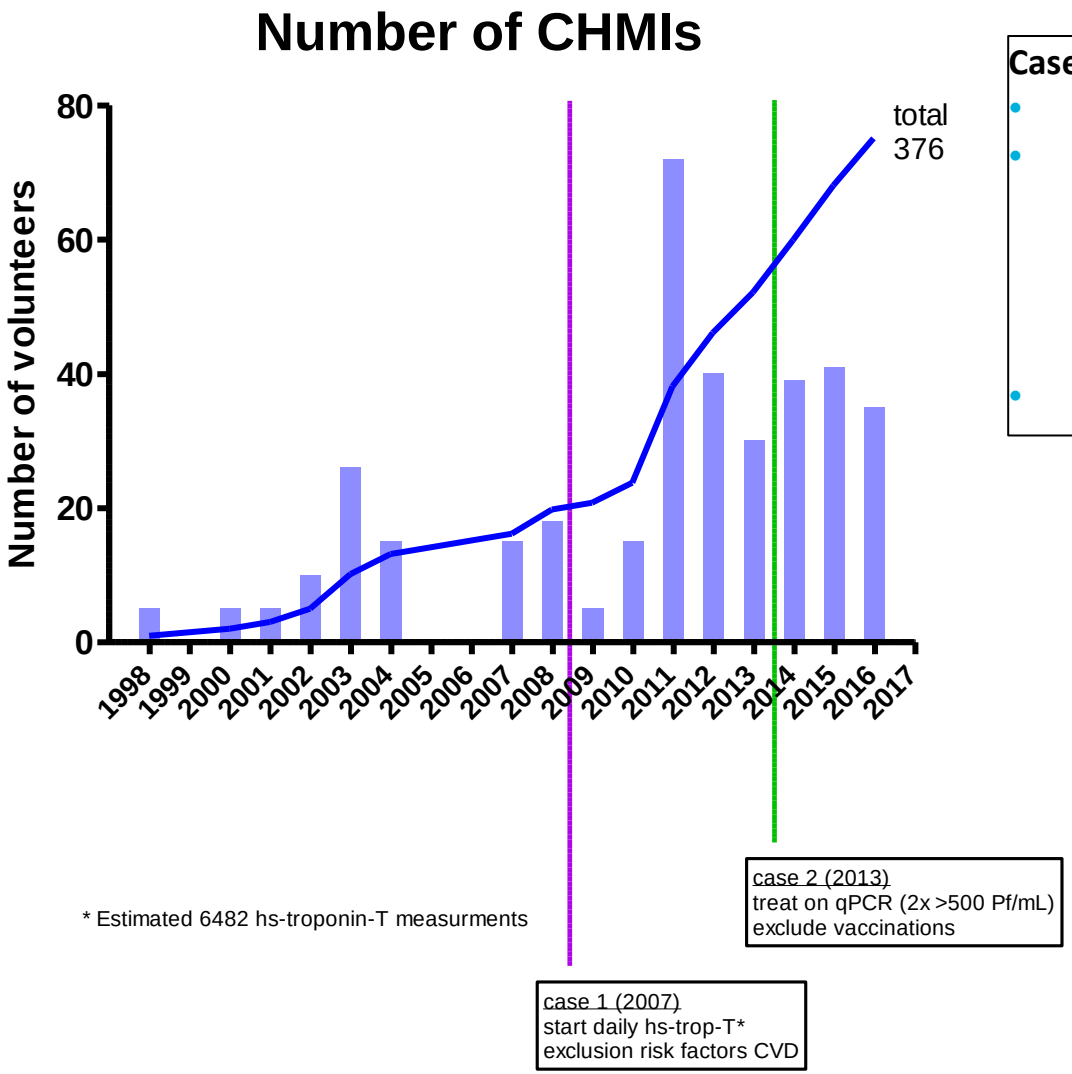
Cardiac events in CHMI



Case 2: Male, 23yrs

- CHMI + Malarone treatement
- Day 13 post CHMI
  - increased troponin-T
  - ECG abnormalities
  - MRI abnormalities
  - retrosternal chest pain (20min)
- Diagnosis: acute myocarditis

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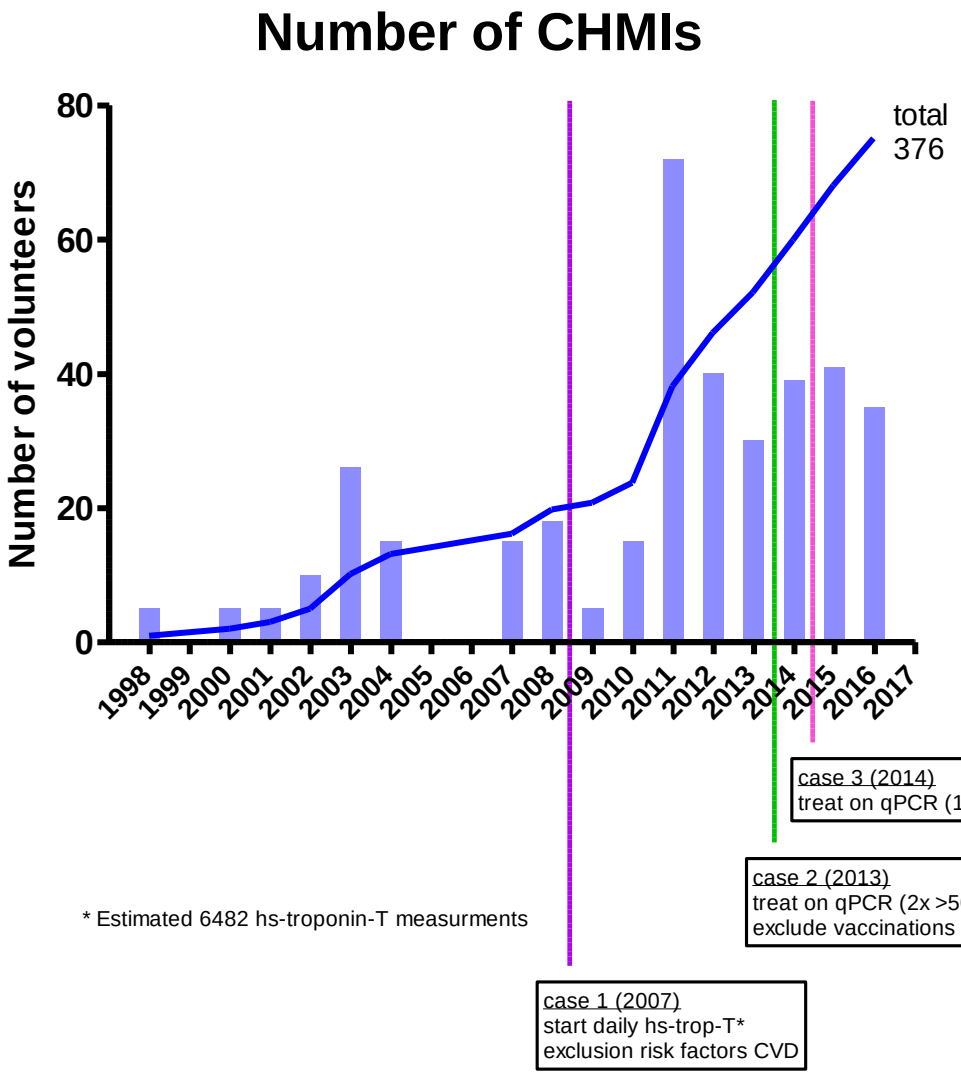
Cardiac events in CHMI



Case 3: Male, 24yrs

- CPS immunization under chloroquine
- Day 10 post 'CHMI'
  - increased troponin-T
  - asymptomatic
  - MRI abnormalities
- Diagnosis: acute myocarditis

SMC: probably related to CHMI

IRB response

- Long term damage?
- Causality and mechanism?
- Can it be predicted and prevented?

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Is there lasting damage?

- Controlled Human Infection Models: healthy volunteers, no benefit
- Instead, disadvantages (symptoms) and risks (unknown prior to trial)

- Balance between risks to volunteers and study benefit
- But, risk must be ‘acceptable’

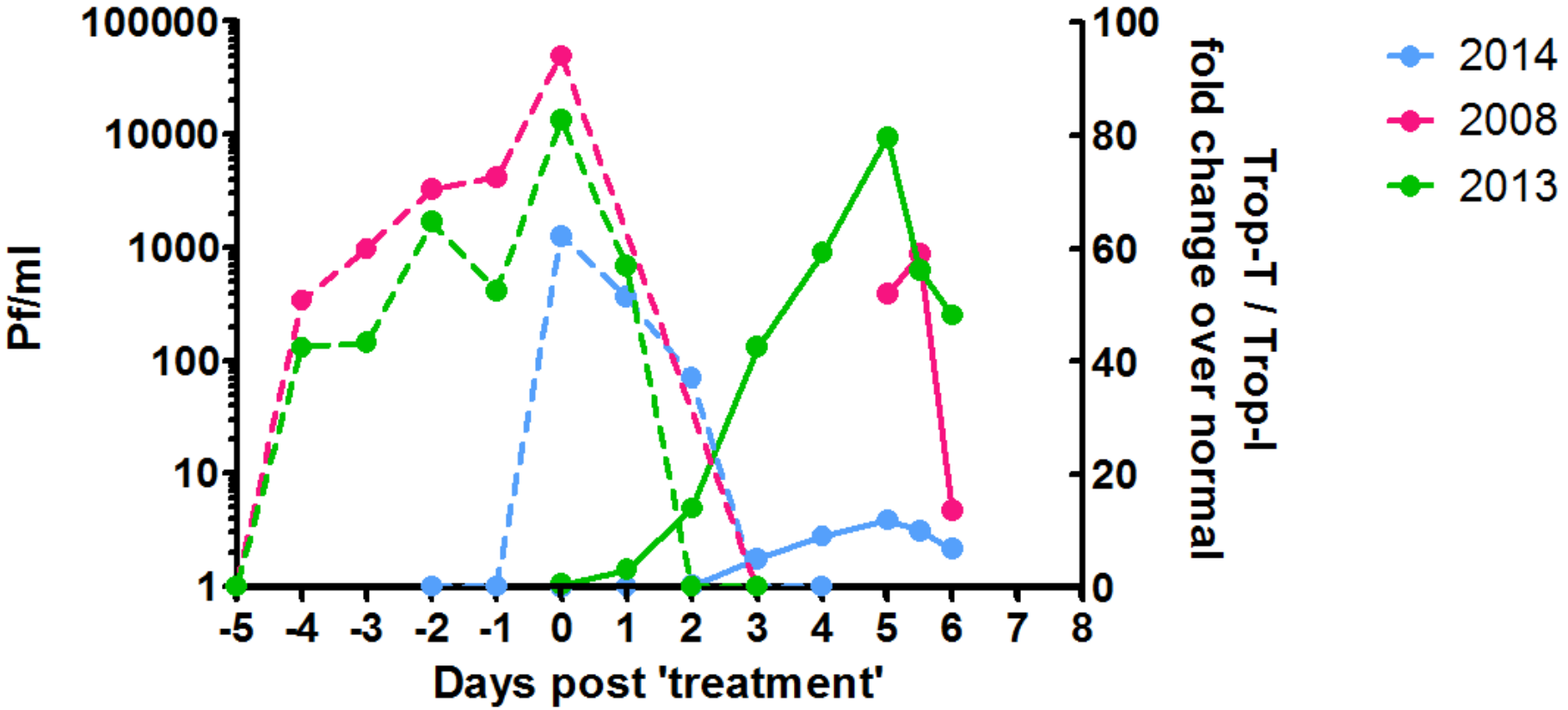
- In these volunteers
  - (Largely) asymptomatic
  - Hospital admission
  - No evidence for functional impairment

- Is this clinically significant?
  Expert opinion: Based on available data, this can be ‘acceptable risk’

Causality and mechanism?

- Three cases out of 376 volunteers, association with CHMI likely
- Incidence of asymptomatic myocarditis in other infections unknown
- Only commonality between the events:
  - Previous parasitemia
  - Treatment

Causality and mechanism?



Causality and mechanism?

- Three cases out of 375 volunteers, similar timing
- Incidence of asymptomatic myocarditis in other infections unknown
- Only commonality between the events:
  - Previous parasitemia
  - Treatment
- Events occur *after* parasitemia
- Without a mechanism, hard to modify or predict the risk

Can it be prevented?

- Can we exclude volunteers ‘at risk’ for a cardiac event?

	2007	**2013**	**2014**
Gender	Female	Male	Male
Age	20	23	24
Medication	Art/Lum	Malarone	Chloroquine
Family history of cardiac disease	Yes	No	No
Concomitant infection	No	Yes (rhinovirus)	No
Concomitant vaccinations	No	Yes	No
Concomitant drug use	No	No	Yes (cannabis)

Increased in- and exclusion criteria to avoid all these possible risk factors.

Can it be prevented?

- A ‘safe’ challenge infection can be terminated in case of severe disease
- But, cardiac events occur *after* treatment

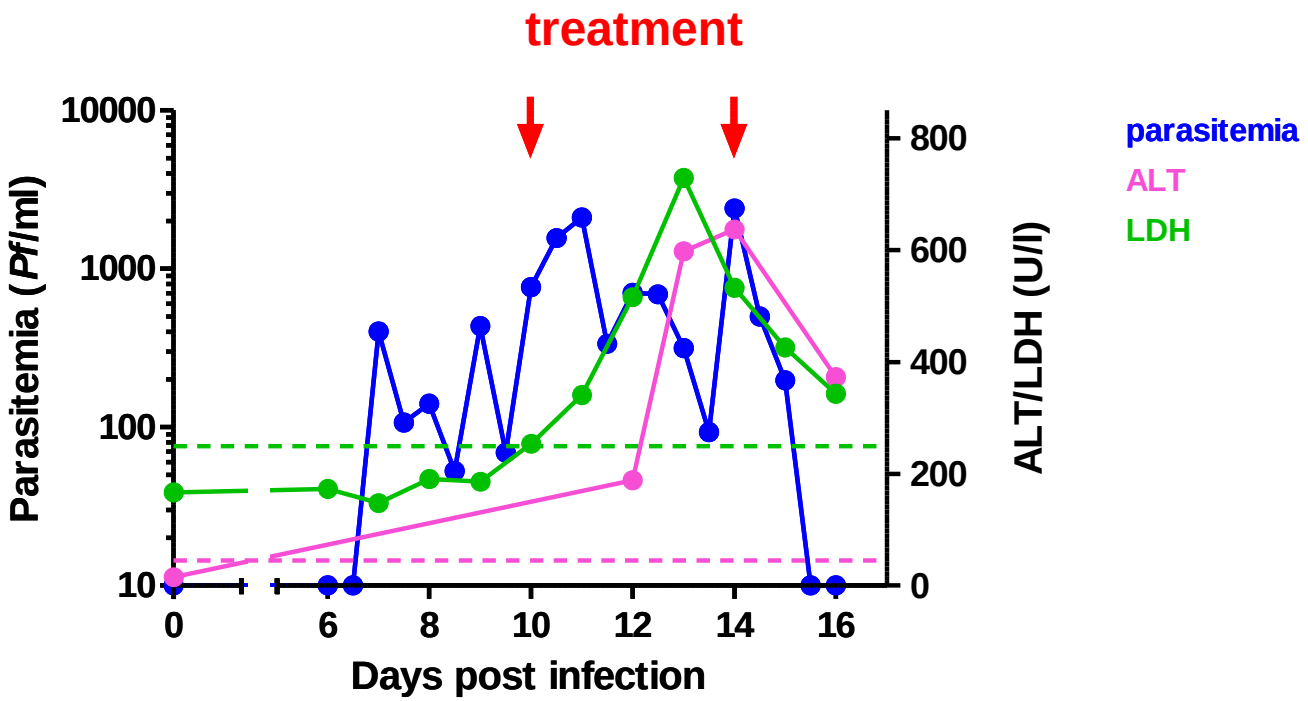
- Can we find a marker that predicts a cardiac event and informs treatment?

CRP D-dimers Platelets Lymphocytes Neutrophils Monocytes	Inflammation
LDH	Damage
Von Willebrand Factor (and others)	Coagulation

Many lab abnormalities in CHMI, but none predict a cardiac event (prior to antimalarial treatment)

Transient liver enzyme elevations

A patient with elevated liver enzymes



Are liver enzymes elevated during CHMI?

- Literature: Liver enzyme abonormalities in uncomplicated malaria

- Analysis of 13 CHMI studies (treatment based on thick blood smear)
  - Many volunteers had some liver enzyme abnormalities
  - Causality unclear (CHMI, medication, concomittent alcohol?)
  - Like cardiac events, not predicted by other laboratory abnormalities

- IRB response
  - Is there lasting damage?
    In all volunteers liver enzymes normalized at 35 days post infection
  - Could CHMI affect other organ systems?

Complete risk analysis

Cardiovascular system
- 3 cases of myocarditis in 376 volunteers, probably related

Liver
- Transaminase abnormalities in all volunteers, causality unclear
- No persistent elevation

Kidney
- Transient, asymptomatic elevations in serum creatinine (within normal limits)
- Normalization on day 35 post infection
- *Expert consultation: Lasting damage is extremely unlikely.*

Skeletal muscle
- Myaglia and LDH elevation common, but never severe abnormalities

Gastro-intestinal tract
- No evidence for damage

Respiratory system
- No evidence for damage

Hematological abnormalities
- Platelet and leukocytes decrease, normalize after several days

Cerebral
- No evidence for complications

Pancreas
- No evidence for complications

Conclusions

- SAEs have an enormous impact on a controlled human infection trial
- Especially if the mechanism is unknown
- Instead, we took broad measures
  - Increase stringency of in- and exclusion criteria
  - Increase monitoring of safety labs
  - Earlier treatment after challenge (if possible)

The CHMI Team

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