The artesunate-amodiaquine fixed-dose combination field monitoring program
Objectives, methods, and first results from Liberia and Senegal

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ASTMH 2009, Washington DC

Artesunate-amodiaquine fixed-dose combination « ASAQ »

– Developed by Sanofi-Aventis and DNDi
  • Once-a-day dosing, 1 or 2 tablets
  • Soluble tablets

– Registered since 2007 in 24 African countries

– Pre-qualified by the WHO in 2008

– Over 20 million treatments distributed in 2009
The ASAQ field monitoring program

**Objective:** proactively gather good quality safety and efficacy data on ASAQ, to quantify potential risks and to document missing information, in a variety of malaria transmission settings

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The ASAQ field monitoring program

**Rationale**

Counterfeits and substandard generics will soon follow ASAQ launch: safety issues, rumors, controversies

**Clinical studies data have limitations**
- Limited patient numbers
- Controlled conditions
- Single malaria episodes

**Limited pharmacovigilance systems in sub-Saharan Africa**
- No pharmacovigilance data from industrialized countries for malaria drugs
  - > 200 million treatments
  - 137 spontaneous reports, 60% from Africa*

* Dec 3, 2008 FDA Advisory Committee Meeting, Bethesda, MD
Artemisinin derivatives safety issues

- Biological
  Transient reticulocytes decreases and transaminases increases

- Neurotoxicity
  Seen with oil-soluble artemisinin derivatives in animals
  A report of irreversible hearing loss after treatment of adult patients with artemether-lumefantrine

- Pregnancy
  Fetal resorption in rodents: not recommended during first trimester of pregnancy

⇒ Risks to be quantified

Amodiaquine safety issues

- Documented issues in prophylactic use
  - 1 in 1,700 serious reactions
  - 1 in 2,200 blood disorders
  - 1 in 15,650 hepatic disorders
  - 1 in 15,650 fatal reactions

- Other issues in malaria treatment
  - Tiredness, nausea, vomiting (malaria symptoms ?)
  - Extra-pyramidal syndromes

⇒ Risks to be quantified
Artesunate + Amodiaquine
Missing information

– Safety of repeated administrations
– Specific populations (HIV/AIDS patients…)
– Second and third trimester of pregnancy
– Safety profile in non parasitemic patients
– Drug interactions
– Interactions with traditional drugs and remedies
– Efficacy in species other than *P. falciparum*

The ASAQ field monitoring program

Objective: proactively gather good quality safety and efficacy data on ASAQ, to quantify potential risks and to document missing information in a variety of malaria transmission settings

Methods
1. Randomized comparative clinical trial
2. Randomized comparative cohort
3. Large-scale safety study
4. “Real life” implementation study
1. Randomized comparative clinical trials

2. Large-scale safety study

3. Randomized comparative cohorts

4. “Real life” implementation study

1. Randomized Comparative Clinical Trials

• Key features
  – Comparative design
  – Laboratory-confirmed malaria
  – Single malaria episodes
  – Clinical and biological safety assessments

• Settings
  Benin (IRD)
  90 ASAQ patients, completed

  Liberia (DNDi, Epicentre, MSF-Switzerland)
  150 ASAQ patients, ongoing analysis

  African multicentric trial (EDCTP)
  1190 ASAQ patients, ongoing analysis
1. Randomized comparative clinical trials
2. **Large-scale safety study**
3. Randomized comparative cohorts
4. “Real life” implementation study

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2. **Large-scale safety study**

**Key features**

- Comparative design: ASAQ vs. AL
- 1000 patients
- Patients > 6 years: able to express subjective symptoms
- Confirmed malaria
- Clinical and laboratory safety assessments

**Setting: Liberia** (DNDi, Epicentre, MSF-Switzerland)

*500 ASAQ patients, ongoing analysis*
Study site

MSF Comprehensive Healthcare Center (CHC), Saclepea, Nimba County, Liberia.

- *Plasmodium falciparum* predominant species of malaria
- Remote, rural region – holoendemic malaria
- “Real life” setting

Objectives

Principal objective

To describe the clinical tolerability of ASAQ in patients ≥ 6 years with uncomplicated *P. falciparum* malaria, compared to AL

Secondary objectives

- Assess efficacy of ASAQ and AL at 28 days
- Assess biological safety
- Day 0 & Day 7 blood levels of desethyl-amodiaquine and lumefantrine.
- Promote awareness of drug safety & pharmacovigilance amongst health-care workers
Study procedures

Collection of adverse events

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<th>Follow up Day</th>
<th>Treatment administration</th>
<th>Symptoms &amp; clinical exam</th>
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Patient disposition

- **Screened**: N = 1254
- **Randomized**: N = 1000
  - ASAQ: N = 498
  - AL: N = 502
- **Exposed**: 498 (100) ASQAQ, 502 (100) AL
- **Participated twice**: 2 (0.4)
- **Safety population**: 496 (99.6) ASQAQ, 502 (100) AL

- **Completed 28 days**: 466 (94.5) ASQAQ, 478 (95.2) AL
- **Premature Discontinuation**: 30 (6) ASQAQ, 24 (4.8) AL
  - LTFU: 7 (1.4), 5 (1)
  - Patient’s request: 1 (0.2), 2 (0.4)
  - Unable to attend: 12 (2.4), 10 (2)
  - Underlying severe hepatitis: 1 (0.2), 0 (0)
  - Other: 9 (1.8), 7 (1.4)

**Study start**: 29.09.2008
**End of recruitment**: 21.04.2009
**End of follow up**: 19.05.2009

Ongoing data analysis
1. Randomized comparative clinical trials
2. Large-scale safety study
3. Randomized comparative cohorts
4. “Real life” implementation study

3. Randomized Comparative Cohort Studies

- **Key features**
  - Comparative design: ASAQ vs. AL
  - Repeated administrations: same treatment for each attack, over a 2-year period
  - Laboratory-confirmed malaria
  - Clinical and laboratory safety assessments

- **Settings**
  - Senegal
  - Uganda

*400 ASAQ patients x n’ malaria attacks*
« SMART-ACCESS » study, Senegal

Dept of Parasitology, UCAD, Dakar University Senegal

Study site: Keur Socé
EIR: 9-12/year
Seasonal transmission
Children and adults
Follow-up Day 28
ECG and audiometric data
August 2007 to January 2009

"SMART-ACCESS" study, Senegal
Patients’ distribution

Number of malaria episodes by treatment group - ITT

Time for recurrence of 2nd episode by treatment group - ITT
A. Yeka, A. Talisuna  
Uganda Malaria Surveillance Project  
Mulago Hospital, Kampala  
Uganda

Study site: Tororo  
EIR > 500 / year  
Children < 5 years at inclusion  
Follow-up Day 42  
Study start June 2008

### « SMART-CURE » study, Uganda  
Enrollment status per number of malaria episodes  
June 2008 - October 2009

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**Total**

3930

End of follow-up planned June 2010
1. Randomized comparative clinical trials
2. Large-scale safety study
3. Randomized comparative cohorts
4. “Real life” implementation study

4. Implementation Study

1. Safety assessment program over 2 years
   To assess
   - ASAQ clinical safety in a health district population
   - Impact of ASAQ deployment on malaria epidemiology over time

2. Nested effectiveness study
   To assess impact of ASAQ deployment on
   - In vivo effectiveness
   - Clinical and biological safety
   - Evolution of parasite resistance
Implementation Study

Safety Assessment Program

• Day 0: All patients attending health centres with suspected uncomplicated malaria attack
  • Prescription of ASAQ
  • Registry for longitudinal malaria prevalence
  • Informed consent for
    – blood smear (post-hoc reading in Abidjan)
    – home visits for safety assessment

• Day 3 to Day 10: trained community health worker visits patient at home to assess tolerability and compliance
  • Simple oral interview (AE report form, number of tablets intake)
  • Referral to health centre if necessary

Implementation study

Nested Effectiveness Study

• **Performed twice**: beginning of the program, and after 18 months of implementation

• **Number of patients**: n = 290 per period

• Study procedures
  – Confirmed malaria diagnosis
  – Supervised intake for first ASAQ dose
  – PCR-adjusted effectiveness assessment Day 28
  – Tolerability assessments
    • Clinical
    • Biological (haematology and biochemical) D0, D3, D14, D28
    – Day 7 desethylamodiaquine assay
    – *In vitro* parasites sensitivity tests (“drug pressure” assessment)

• **Started October 2009**
ASAQ clinical study sites

ASAQ field monitoring program
Total expected database

Comparative clinical trials:  > 2800 ASAQ patients

Comparative cohort studies :  400 ASAQ patients
x n malaria attacks

Implementation study :  ~ 15,000 ASAQ-treated malaria attacks

TOTAL  ~ 20,000 case reports
ASAQ field monitoring program

Key Stakeholders

- National Malaria Control Programs
- National Pharmacovigilance Units
- Independent Safety Monitoring Board
- WHO Department of Medicines Policy and Standards:
  - ASAQ Risk Management Plan submitted March 2009

Conclusion
ASAQ field monitoring program

Key Features

- Variety of study designs and malaria transmission settings to address multiple issues and information gaps = shed light from different angles on ASAQ efficacy and safety

- 1st Risk Management Plan submitted to the WHO

- 1st Risk Management Plan set up entirely in Africa

- Dynamic program

Conclusion: our objectives

• **Short-term:** design innovative ways of collecting quality data on ASAQ safety and efficacy

• **Medium-term:** contribute to the design of Risk Management Plans for future new antimalarials

• **Longer term:** beyond antimalarials, contribute to strengthening of pharmacovigilance systems in Africa, adapted to the needs and resources of the countries
Acknowledgments

• National Malaria Control Programs

• National Pharmacovigilance Units

• Clinical experts, pharmacovigilance experts, etc.

• Dr Valérie Lameyre, Brigitte Charron, Tina Olympio