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

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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

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

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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

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

<table>
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<tr>
<th>Follow up Day</th>
<th>Treatment administration</th>
<th>Symptoms &amp; clinical exam</th>
<th>AST/ALT Biochemistry</th>
<th>Full blood count</th>
<th>Blood smear</th>
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Patient disposition

Study start: 29.09.2008
End of follow up: 19.05.2009

Screened N=1254
Randomized N=1000

ASAQ N=498
AL N=502

Exposed
Participated twice
Safety population:
• Completed 28 days
• Premature Discontinuation:
  LTFU
  Patient’s request
  Unable to attend
  Underlying severe hepatitis
  Other

498 (100) 502 (100)
2 (0.4)     0 (0)
496 (99.6) 502 (100)
466 (94.9) 478 (95.2)
30 (6)      24 (4.8)
7 (1.4)     5 (1)
1 (0.2)     2 (0.4)
12 (2.4)    10 (2)
1 (0.2)     0 (0)
9 (1.8)     7 (1.4)

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

| Date       | E1 | E2 | E3 | E4 | E5 | E6 | E7 | E8 | E9 | E10 | E11 | E12 | E13 | E14 | E15 | E16 | E17 | E18 | E19 | Total |
|------------|----|----|----|----|----|----|----|----|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-------|
| 16/01      | 413| 383| 345| 279| 217| 127| 73 | 29 | 9  | 1   | 1876 |
| 06/02      | 413| 386| 362| 306| 258| 162| 104| 59 | 22 | 5   | 2077 |
| 07/03      | 413| 388| 370| 325| 286| 194| 129| 80 | 42 | 15  | 2245 |
| 01/04      | 413| 389| 382| 340| 319| 243| 177| 116| 76 | 39  | 15  | 2515 |
| 23/04      | 413| 390| 388| 347| 339| 258| 219| 145| 101| 65  | 11  | 2   | 2706 |
| 27/04      | 413| 394| 394| 358| 356| 301| 259| 206| 149| 104 | 31  | 18  | 2   | 3054 |
| 01/05      | 413| 394| 394| 371| 356| 316| 285| 247| 198| 141 | 97  | 59  | 29  | 14  | 3   | 1   | 3318 |
| 04/06      | 413| 394| 394| 375| 363| 334| 308| 262| 227| 184 | 133 | 83  | 53  | 31  | 12  | 4   | 1   | 3571 |
| 01/07      | 413| 394| 394| 377| 368| 342| 320| 282| 244| 200 | 163 | 74  | 41  | 25  | 12  | 4   | 1   | 3771 |
| 30/09      | 413| 394| 394| 378| 372| 347| 328| 295| 261| 218 | 182 | 136 | 93  | 59  | 34  | 18  | 7   | 1   | 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
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