PARTNERSHIPS IN ACTION

Efficacy and safety monitoring in the field: The artesunate-amodiaquine fixed-dose combination monitoring plan

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Available clinical data on artesunate (AS)-amodiaquine (AQ) association

- **AS + AQ loose combination: 8309 patients**
  - Review of 30 studies (P. Olliaro et al) : 11571 patients, of which 5272 AS+AQ
  - Ph. Brasseur et al : 3037 patients included over 6 years

- **ASAQ fixed-dose combination : 1003 patients**
  - 750 randomized patients: ASAQ (n= 375) vs. AS+AQ (n= 375) Burkina Faso (Sirima et al)
  - 941 randomized patients, Senegal, Mali, Cameroon, Madagascar ASAQ (n = 628) vs. AL (n = 312)

Artemisinin derivatives safety issues

- Biological
  - Cases of transient decreases in number of reticulocytes and increase in transaminases
- Pregnancy
  - Fetal resorption in rodents: not recommended during first trimester of pregnancy
- Neurotoxicity
  - A report of irreversible hearing loss after treatment of adult patients with artemether-lumefantrine (oil-soluble artemisinin derivatives ?)

Amodiaquine safety issues

- Haematological
  - Severe neutropenia : mainly with anti-inflammatory doses for rheumatoid arthritis,
  - Agranulocytosis (3 to 24 weeks exposure range)

- Liver toxicity
  - Mainly in case of prophylactic use
  - Few cases of hepatitis and asymptomatic increases in liver enzymes in curative use

- Other, less well documented issues
  - Tiredness (malaria symptoms ?)
  - Nausea, vomiting (malaria symptoms ?)
  - Extra-pyramidal syndromes

Ghana, January 2006

- Press reports 70 cases of Adverse Drug Reactions (ADR) with AS+AQ: insomnia, general weakness, dystonia, red itchy eyes, restlessness

  Four reports of « weakness and writhing movements of the face, hands and eyelids and involuntary protrusion and spasms of the tongue as well as inability to talk »

- National Pharmacovigilance centre: 55 reported ADR
  - 12 dystonias and extrapyramidal reactions
  - 11 restlessness
  - 24 gastrointestinal symptoms, general weakness and fatigue

- Related with 6 brands of locally-produced AS+AQ combinations (fixed-dose combinations, co-blisters).

Lessons learned

- **Issues with Amodiaquine safety**
- **Not all drugs labeled as “artesunate-amodiaquine” are real “artesunate-amodiaquine”**
- **Pharmacovigilance requires good data**
  - Drug actually taken (exact dose ± impurities, excipients, etc.)
  - Concomitant medications (including traditional remedies)
  - Concomitant conditions
  - Denominator
  - Etc.

The ASAQ (Coarsucam) Monitoring Plan

"ASAQ" post-launch action plan
Rationale

- Counterfeits and substandard generics will soon follow ASAQ launch
  - Risk of safety issues, rumors, controversies

- Limited pharmacovigilance and resistance monitoring systems in sub-Saharan Africa
  - Limited spontaneous pharmacovigilance reporting
  - No pharmacovigilance data to be expected from industrialized countries

- Sanofi Aventis and DNDi have a duty to monitor ASAQ safety, as well as development of resistances during wide-scale deployment

ASAQ post-launch key issues

- **Safety**
  - Confirm ASAQ safety profile in larger numbers of patients
  - More data on adult patients
  - Repeated administrations
  - Co-administered treatments
  - Concomitant conditions
  - Safety in first trimester of pregnancy
- **Efficacy / effectiveness in various geographic areas**
- **Development of parasite resistance**

ASAQ monitoring plan
Overview

Objective : gather quality safety and efficacy data

- in various malaria transmission settings
- through various proactive studies

Methods

1. Randomized comparative clinical trials
2. Randomized comparative cohort studies
3. Implementation studies

Randomized Comparative Clinical Trials

Randomized Comparative Clinical Trials
Efficacy & Safety « Investigator-Sponsored Trials»

- **Benin** (IRD, Ph Deloron)
  - Open, randomized, AL versus SP versus ASAQ
  - Children under 10, n = 225
  - ***90 ASAQ patients, ongoing analysis***

- **African multicentric trial** (EDCTP, U. D'Alessandro)
  - Burkina Faso, Nigeria, Zambia, Gabon, Uganda, Mozambique
  - Open, randomized, ASAQ versus AL versus DHAPQ
  - Children < 5 years
  - Follow-up 6 months; up to 2 malaria attacks treated
  - ***1190 ASAQ patients, ongoing enrollment***

- **Liberia** (DNDi, Epicentre, MSF-Switzerland)
  - Randomized, open-label comparative study, ASAQ vs. AL
  - 300 patients< 5 years
  - ***150 ASAQ patients, ongoing enrollment***

Randomized Comparative Clinical Trials
Safety-focused « Investigator-Sponsored Trial »

- **Liberia (DNDi, Epicentre, MSF-Switzerland)**
  - Patients ≥ 6 years
  - Randomized, open-label comparative study, ASAQ vs. AL
    - 1000 patients
    - Confirmed malaria diagnosis, slide or RDT
    - Active clinical safety assessment up to Day 7
    - Passive reporting of AEs until day 28
    - Efficacy assessment day 28
    - PK DSAQ or L day 7
    - ***500 ASAQ patients***

Randomized Comparative Cohort Studies

Randomized Comparative Cohort Studies

- Primary objective : assess impact of repeated ASAQ administrations on efficacy and safety

- Design : randomized , comparative, longitudinal studies. N = 2 x 200 patients

- Each malaria attack occurring during 2 years treated by either ASAQ or artemether-lumefantrine (AL)

Randomized Comparative Cohort Studies

- **Compare impact of repeated administrations of ASAQ and AL on**
  - Efficacy (1st episode)
  - Effectiveness (other episodes)
  - Clinical and biological tolerability

- **Sites :**
  - **Uganda** (children < 5)
  - **Senegal** (adults and children)
    - ECG and audiometric in patients ≥12 years

400 ASAQ patients x n' attacks

Implementation Study

Implementation Study

Setting

- Selected community health centres in a pilot Côte d'Ivoire district
  - ASAQ reliably available
  - Sedentary population, good attendance rate at health centres
  - Documented " clinical malaria" epidemiological profile at baseline
- Monitored population: approx. 7000 attendees/ year

Implementation Study

Objectives

Over 2 years, assess impact of ASAQ usage, in “real life” conditions, on

- ASAQ clinical and biological safety
- ASAQ effectiveness
- Evolution of parasite resistance
- Malaria epidemiology over time
- Patient compliance

Implementation Study
Design

1. All patients with clinical diagnosis of malaria
   - Treated with ASAQ
   - Blood smear for *ex post* analysis
   - Visited at home within 1 week

2. Nested efficacy and safety study in 290 patients with confirmed malaria diagnosis

Implementation Study

Main study outcomes

– **Clinical safety**

- Active recording at patients' home by trained health workers
- Malaria-proven patients vs. non malaria patients (*ex post*)

– **Malaria epidemiology over time**

- Evolution of uncomplicated and complicated malaria incidence over time : malaria cases registries in health centres

Implementation Study
Nested Safety and Effectiveness Study

- **Performed twice : program start, and after 18 months**
- **N = 290 patients per period**
- **Study procedures**
  - Informed Consent
  - Confirmed diagnosis by thick smear (+ count)
  - Supervised intake for first ASAQ dose
  - Follow-up : D28
  - PCR adjusted effectiveness
  - Tolerability
    - Clinical
    - Biological (haematology and biochemistry)
  - D7 desethylamodiaquine assay: tbd
  - *In vitro* parasites sensitivity tests (“drug pressure” assessment)

Implementation Study
Key Stakeholders

- Côte d'Ivoire National Malaria Control Program
- Côte d'Ivoire National Pharmacovigilance Centre
- Agboville district health centres
  - Physicians
  - Nurses
  - Community health workers
- Independent Data Safety Monitoring Board
- *Medicines for Malaria Venture* and *DNDi*

Conclusion

ASAQ monitoring plan

Expected database

Comparative clinical trials: **1800 ASAQ patients**

Comparative cohort studies : **400 ASAQ patients x n malaria attacks**

Implementation study : **~ 15,000 malaria attacks**

ASAQ Monitoring Plan
Objectives

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

- **Medium-term :** test methods for risk management plans for new antimalarials

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

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Impact malaria
sanofi aventis *s'engage*

Medicines for Malaria Venture