Active surveillance of antimalarials: case study from Nigeria

Peter U. Bassi, MBBS MSc FMCP(Niig)
University of Maiduguri, Nigeria.
(Member national Drug Safety Advisory Committee)
Active Surveillance

- Active surveillance in contrast to passive surveillance seeks to ascertain completely the ratio/number of ADRs via a continuous preorganized process. It can obtain comprehensive data on individual adverse reports.

Examples of these methods include: Prescription event monitoring (drug event monitoring), Record linkage, Registries, Case control studies and Cohort event monitoring (CEM).

- CEM: Is a prospective, observational study that involves formal and continuous monitoring for the purposes of generating signals or evaluating and confirming hypothesis related to medicine and event(s). It is a prospective study(ies) of a reasonably sized cohort exposed to treatments and assessed for any subsequent AEs.

- Monitor relatively common events
  - Regular collection of health outcomes
  - Determine rates of adverse events
  - Organized data collection from health care providers, often from sentinel site facilities.
CEM in determining AE profile and long-term toxicities of ACTs

Advantages

- The ability to produce rates;
- The ability to produce a near complete profile of the AEs and/or ADRs for the medicines of interest;
- Very effective in identifying signals at an early stage;
- The ability to produce rapid results in a defined population;
- The method provides sound evidence with which to deal with any drug scares.

Disadvantages

- The method is more labour intensive and more costly than spontaneous reporting.
- It will be new to health professionals and Pharmacovigilance Centres and training in its use will be necessary.
- A major challenge for such prospective cohort studies is the identification of treated (exposed) patients.
- This method of pharmacovigilance is difficult, even in countries with a well-developed health care system.
CEM: a case study from Nigeria

OVERALL OBJECTIVES
To evaluate safety in the use of ACTs among populations in Nigeria and develop the safety profile of ACTs used in Nigeria mainly; Artemether-Lumefantrine (AL) and Artesunate-Amodiaquine (AA)

SPECIFIC OBJECTIVES:
- Obtain information on AEs in ACT users
- Establish causality relationship between observed AEs and use of ACTs
- Early characterization of Adverse Events (AEs) profile of ACTs
- Generate data for decision making
- Obtain cohort for future studies
METHODOLOGY

A pilot of a cohort CEM programme evaluate and document AEs that could result from the use of two combinations of artemisinin derivatives: AL and AA approved by FMoH for treatment of uncomplicated malaria in Nigeria.

DESIGN

- The study was prospective and observational with patients being observed under real life conditions.
- Patients were given a standard course of ACTs to be taken over three days and were asked to return for follow-up assessment on days 3 and 7 after commencement of treatment.
- Patients who did not return were followed up at home or contacted by telephone.
**METHODOLOGY**

**POPULATION**

A cohort of 3000 was achieved by enrolment of patients treated with either AA or AL until 500 patients were obtained at each site.

Patients presumptively diagnosed with malaria and given ACTs were enrolled consecutively irrespective of age, sex, presence of other disease conditions and use of other medicines.

Enrolment of patients was performed by trained personnel at each facility from January – April 2009.

Patients were given AA or AL according to local clinical practice without pre-allocation of respective numbers.

**SITES:** 6 sentinel sites spread across the 6 geopolitical zones of the country as shown on map.

*Map of Nigeria showing the CEM study sites*
METHODOLOGY

ADVOCACY and PERMISSION

Advocacy visits were undertaken to various stakeholder groups including the FMoH and heads of the relevant health institutions.

Ethical clearance was obtained from the National Health Research Ethics Committee (NHREC).

Data Collection and analysis

Any AEs reported by patients on questioning were recorded using specially designed pre- and post-treatment questionnaires.

- They were asked to record only new events since the commencement of treatment or previously existing events that had become worse.

- The WHO definition of AE was used: Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

- Statistical analyses were carried out using simple frequency distribution, percentages, and Chi Square analysis to study relationships. Graphs and tables were employed to present the results.
**PATIENT FOLLOW-UP**

<table>
<thead>
<tr>
<th>Patients</th>
<th>AA (%)</th>
<th>AL (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients enrolled</td>
<td>1919(63.7)</td>
<td>1068(35.5)</td>
<td>3010 (100)</td>
</tr>
<tr>
<td>Total number of patients who returned for 1st FUV</td>
<td>1259(43.4)</td>
<td>1638(56.4)</td>
<td>2904 (96.5)</td>
</tr>
<tr>
<td>Total number of patients who returned at the 2nd FUV only</td>
<td>32(54.2)</td>
<td>24(40.7)</td>
<td>59 (2.0)</td>
</tr>
<tr>
<td>Total number of patients seen at follow-up</td>
<td>1578(53.3)</td>
<td>1385(46.7)</td>
<td>2963 (98.4)</td>
</tr>
<tr>
<td>Total number of patients who were lost to follow up</td>
<td>30(63.8)</td>
<td>17(36.1)</td>
<td>47 (1.6)</td>
</tr>
</tbody>
</table>
Pattern of Symptoms at Presentation

- Fever: 2231
- Headache: 1437
- Body pain: 864
- Loss of appetite: 879
- Bitter taste: 552
- Body weakness: 605
- Joint pain: 580
- Cough: 477
- Diarrhoea: 189
- Chills/Rigors: 224
- Nausea: 193
- Vomiting: 356
- Abdominal pain: 429
- Dizziness: 236
New/worsening (Persisting) events at 1st FUV

Adverse Events

- ABDPAIN
- LOSS OF APPETITE
- BODY PAIN
- BITTERNESS OF MOUTH
- CHILLS/RIGOUR
- COUGH
- DIARRHEA
- DIZZINESS
- FEVER
- HEAD ACHES
- JOINT PAIN
- NAUSEA
- VOMITING
- WEAKNESS

Frequency

- AA
- AL
New /worsening (Persisting) events at 2nd FUV
## Adverse Events at 1st and 2nd Visits

<table>
<thead>
<tr>
<th>Events</th>
<th>AL (%)*, n = 174</th>
<th>AA(%)*, n = 1295</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>21 (12.1)</td>
<td>224 (18.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>20 (11.5)</td>
<td>47 (3.6)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>11 (6.3)</td>
<td>77 (6.0)</td>
</tr>
<tr>
<td>Fever</td>
<td>8 (4.6)</td>
<td>20 (1.5)</td>
</tr>
<tr>
<td><strong>Alimentary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>15 (8.6)</td>
<td>93 (7.2)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>15 (8.6)</td>
<td>60 (4.6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14 (8.1)</td>
<td>133 (10.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (4.0)</td>
<td>28 (2.2)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>4 (2.3)</td>
<td>34 (2.6)</td>
</tr>
<tr>
<td>Bitter taste/Sore mouth</td>
<td>2 (1.2)</td>
<td>6 (0.5)</td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weakness</td>
<td>44 (25.3)</td>
<td>478 (36.9)</td>
</tr>
<tr>
<td>Body Pains</td>
<td>6 (3.5)</td>
<td>69 (5.3)</td>
</tr>
<tr>
<td>Joint Pains</td>
<td>1 (0.6)</td>
<td>9 (0.7)</td>
</tr>
<tr>
<td><strong>Dermatological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rashes/Itching</td>
<td>6 (3.5)</td>
<td>17 (1.3)</td>
</tr>
</tbody>
</table>
SUMMARY

- Most common Adverse Events (AEs) observed in the Cohort are:
  - General body weakness - 36.9/25.3% (AA/AL);
  - Dizziness - 18.8/12.1% (AA/AL);
  - Vomiting - 10.3/8.1% (AA/AL);
  - Abdominal Pain - 7.2/8.6% (AA/AL);
  - Insomnia - 6.0/6.3% (AA/AL);
  - Body pains - 5.3/3.5 (AA/AL)% and
  - Anorexia - 4.6/8.6 (AA/AL)%.

- Mean Duration of illness (events) is 3 days.
• **Summary/conclusion**
  - Good response rate (97.5%) was recorded
  - Adherence to study protocol was good (> 63%)
  - Most sites reached their recruitment target of 500 patients at end of the study
  - Observed AEs similar to ADR profile of ACTs reported in literature with few documented rare AE such as .... (please provide from data) also observed
  - Patients treated with AA had more AEs but had better treatment outcome
  - 2 patients on AA had life threatening AEs, 1 patient each on AA and AL experienced prolonged hospital stay

• **Challenges**
  - At the commencement of the programme because of fear by some patients, Physicians splitting the dose of AA and the effect it had on the study findings
  - Empty fields especially in patients with no complaints -
  - no data collected on events experienced 7 days before treatment initiation visit thus making it not possible to make comparisons
  - The relatedness of the AE and use of drug was not done i.e. no causality assessment done so far.
Implication of study findings in treatment guideline update and clinical practices

- CEM can help in identifying AEs following use of ACTs
- ACTs is a common reason for treatment interruptions in malaria treatment in Nigeria.
- The study suggest that ACTs are effective as evidence by > 90% treatment outcome of Malaria symptoms.
- This pilot CEM programme suggests that adverse events with ACTs are common however, severe adverse events were not common occurrence in the observed cohort
- It appears that ACTs have a tolerable safety profile among Nigerians.
- A larger cohort will be helpful to establish statistical significance of findings and probably identify rare AEs.
Scale up

CEM scale commenced in January 2012, - same methodology as pilots,

1. Sites for Programme: carried out at 18 health care facilities spread in six geopolitical zones of the country on the basis of 3 per geo-political zone.

2. Engagement of community pharmacies: Recognizing that a considerable number of Nigerians seek treatment from the private sector through community pharmacies/patent medicine vendors/drug hawkers,

3. Enrolment of Patients (Inclusion Criteria): 1. A total cohort of 10,000 additional patients will be enrolled.

4. Ethical Clearance: Was obtained from NHREC due to the public health importance of the programme.

5. Coverage and Duration: The scale up programme is proposed to cover a total of 18 healthcare facilities servicing urban and rural populations.
QUESTIONS???

THANK YOU FOR LISTENING
ACKNOWLEDGEMENTS

1. Dept. of medicines policy and standard quality assurances and safety medicines, WHO - Geneva, Switzerland
2. Mary Couper
3. David Coulter
4. Shanthi Pal
5. Magnus Wallberg
6. NPC, NAFDAC - Nigeria
7. National Malaria Control Programme, FMoH - Abuja
8. Society For Family Health, Abuja-Nigeria
9. Yakubu Gowon Centre, Nigeria
10. Pharmacovigilance of Antimalarial