Pharmacovigilance

Investigator Meeting

1st May 2015, University of Birmingham Medical School

BIRMINGHAM CLINICAL TRIALS UNIT

UNIVERSITY OF BIRMINGHAM

Hull and East Yorkshire Hospitals NHS Trust

NHS

Definitions – Adverse Event

- Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment

<u>In STOP-ACEi</u>

- Reported for duration of patient trial participation
- Reported on CRF for next trial visit

Definitions – Adverse Reaction

- Any untoward response in a participant to an investigational medicinal product which is related to any dose administered to that participant.
- Relatedness must be determined by medically qualified personnel.

<u>In STOP-ACEi</u>

- The IMPs are:
  - Any ACEi/ARB used in control arm
- Also consider:
  - ACEi/ARB discontinuation in experimental arm
- Reporting – same as for adverse events

Definitions – Serious

- Any adverse event or reaction that:
  - Results in death
  - Is life-threatening
  - Requires hospitalisation or prolongs existing hospitalisation
  - Results in persistent or significant disability or incapacity
  - Consists of a congenital anomaly or birth defect

<u>In STOP-ACEi</u>

- Standard definitions used.
- Reported on an SAE form by fax.

Definitions – Unexpected

- An adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product set out in the SmPC or IB for that product.

<u>In STOP-ACEi</u>

- Use SmPC for ACEi or ARB
- Use protocol for discontinuation of ACEi or ARB
  - Hypertension
  - Increased peripheral oedema
  - Gout
  - Change in proteinuria
  - Hypokalaemia
  - Weight gain
  - Increase in breathlessness
- Most events/reactions will be expected

Reporting – why?

Why are we reporting adverse events for STOP-ACEi?

- Secondary outcome:

  To test that withdrawal of these treatments does not cause excess harm (e.g. increased cardiovascular events such as heart failure, hypertension, myocardial infarction, stroke) and is not associated with an increase in adverse effects.

- To add to the safety profile of the drugs/intervention and comply with the regulations

Reporting – what?

What adverse events are we reporting for STOP-ACEi?

- All AEs should be reported on the visit CRF and in medical notes
  - Whether serious or not
  - Whether expected or not
- SAEs (including SUSARs) should also be reported on an SAE form and faxed to BCTU within 24 hours of being notified of the event
- SAEs that don't need to be reported on an SAE form
  - Hospitalisations for:
    - Routine treatment or monitoring of the studied indication that is not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened

Reporting – how?

CRFs

Non-serious

Serious

Fax – 0121 415 9135
Within 24 hrs of notification

CI

Sponsor

DMC

MREC

MHRA

Oversight

- The Data Monitoring and Ethics Committee
  - Trial Statistician
  - Consultant Cardiologist
  - Consultant Nephrologist
- Purpose
  - To safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, ensure the trial collects the necessary information to address the trial question and monitor the overall conduct of the clinical trial.
- Data reviewed:
  - Patient safety
  - Treatment efficacy
  - AEs/SAEs
  - Data return rates
  - Recruitment
  - Data quality

Table of Causality

Category	Definition
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration or discontinuation of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events)
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration or discontinuation of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments)
Not related	There is no evidence of any causal relationship

Issues for STOP-ACEi - Causality

- Assessment of causality will determine if a serious event is an SAE or an SAR

- Is the event related to ACEi/ARB withdrawal or CKD?
  - Consider timeline
  - Protocol guidance: within 3 months of withdrawal is more likely to be a reaction to withdrawal
- Existing evidence suggests no difference in CV events when using ACEi/ARB therapy vs. non-ACEi/ARB therapy to control BP
- DMEC will be best placed to determine if there is a causal relationship – whole population data vs. single event reporting

Issues for STOP-ACEi - Expectedness

- Assessment of expectedness will determine if a serious event is an SAE or a SUSAR

- What do we expect when withdrawing ACEi/ARB?
  - Increased CV events?
  - Hypertension?
- Disease progression may confound assessment
- Blood pressure should remain controlled with other antihypertensives

Expected effects of ACEi or ARB

- Skin rashes
- Dizziness
- Altered taste sensation
- Headache
- Sinusitis
- Dyspepsia
- Diarrhoea
- Constipation
- Myalgia

Events possibly expected from discontinuation of ACEi or ARB or combination of both

1. Hypertension
2. Hypokalaemia
3. Increased peripheral oedema
4. Gout
5. Change in urinary proteinuria
6. Weight gain
7. Increase in breathlessness

Cardiovascular events: (myocardial infarction (MI), stroke and heart failure)

- could potentially be expected from ACEi/ARB withdrawal but may equally be expected from progression of the patient's CKD.
- cardiovascular events occurring within the first 3 months of ACEi/ARB withdrawal could be related to ACEi/ARB withdrawal and cardiovascular events occurring after 3 months of ACEi/ARB withdrawal are related to the patient's disease progression.

Issues for STOP-ACEi – Heart Failure

- Defining heart failure presents particular problems
- STOP-ACEi is open-label
  - Opportunity for bias to affect assessment
- E.g. a patient that you know has recently stopped ACEi/ARB treatment complains of increased breathlessness.
  - Is this heart failure?
  - Is your decision affected by knowledge of ACEi/ARB withdrawal?
- Bias in assessment leads to bias in incidence between groups
- Need for clear definitions

Issues for STOP-ACEi – Heart Failure

Framingham criteria

Major criteria	Minor criteria
Paroxysmal nocturnal dyspnea	Bilateral ankle oedema
Neck vein distention	Nocturnal cough
Rales	Dyspnea on ordinary exertion
Radiographic cardiomegaly	Hepatomegaly
Acute pulmonary oedema	Pleural effusion
S3 gallop	Decrease in vital capacity by one third from max recorded
Increased central venous pressure (>16 cm H2O at right atrium)	Tachycardia (heart rate>120 beats/min.)
Hepatojugular reflux	
Weight loss >4.5 kg in 5 days in response to treatment	

- CHF = simultaneous presence of at least 2 major criteria **OR** 1 major with at least 2 minor
- Minor criteria are acceptable only if they cannot be attributed to another medical condition
- Criteria may need to be recorded on CRF

DMEC Members & Trial Steering Committee

Dr John Firth (Chairman), Consultant Nephrologist, Addenbrooke's Hospital, Cambridge
Dr Paul Kalra, Consultant Cardiologist, Queen Alexandra Hospital, Portsmouth Hospitals NHS Trust
Mrs Merryn Voysey, Senior Trial Statistician, Primary Care Clinical Trials Unit, University of Oxford

Richard Haynes, Consultant Nephrologist, Oxford
Sunil Bhandari, Consultant Nephrologist, Kingston upon Hull
Arif Khwaja, Consultant Nephrologist, Sheffield
Nick Selby, Independent Physician, Consultant Nephrologist, Derby
Christopher Allison, Patient Representative.