The bottom line of safety data analyses: practical experiences in the characterisation of drug safety profiles

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Overview

• Introduction
• Pieces of a puzzle
• Pearls of practice
Beate Aurich considers not having a conflict of interest for this presentation. She has been invited by Cytel to present at this conference. She works since October 2015 as a Project Leader in the Department of Paediatric Clinical Pharmacology at Robert Debré Hospital in Paris. Between 2006 and 2015 she has worked as a pharmacovigilance physician for GlaxoSmithKline and Novartis. She currently holds GSK shares.
Introduction

Ultimate goal of all pharmacovigilance activities is to

- Inform patients and health care professionals of adverse drug reactions (ADRs)
- Reduce the risk of ADRs
- Ensure a favourable benefit-risk balance is maintained
Data sets/ databases
- Clinical trials
- Observational studies
- Spontaneous reports

Signal detection
Data → Signal

Signal evaluation/ causality assessment

Related
Signal → ADR

Not related
Adverse event (AE), not related

- Pre-clinical data
- PK/PD data
- Literature
- Class effects
- EHR data
- Epidemiological data

- Label/
  Package insert
- Investigator brochure

Insufficient/ inconclusive data
Pharmacovigilance takes into consideration

Data - Capture
  (e.g. why, how, when, by whom, where, what)

- Transformation
  (e.g. coding, data basing)

- Analysis
  (e.g. pooling, grouping, stratification, meta-analyses)
Example: Factors influencing AE/ADR reporting include

- **Severity of treated condition and comorbidities**
  - Different reporting of AEs/SAEs (e.g. patient in intensive care vs mild asthmatic)
- **Information**
  - Distinguishing ADRs from disease related AEs can be difficult at an individual patient level (e.g. pneumonia in a patient with leukaemia)
- **Reporter’s view on the safety profile**
  - AE/SAEs considered not drug related may not be reported (particularly challenging for syndromes)
• **Communication**
  – HCP may consider AE/SAE not relevant (e.g. no treatment required) > no reporting
  – Perceived administrative burden with ADR reporting may discourage reporting
  – Patients may not report because they worry the drug may get stopped, may not consider the event relevant, don’t want to burden the HCP
  – Patients may be unable to communicate (e.g. intubated patients, young children)

• **Health care setting**
  Diagnostic criteria and description of medical conditions may vary between HCPs, countries, regions:
  * Diagnostic criteria for community acquired pneumonia
    > With or without chest X-ray
  * Description of abnormal liver function:
    > Anglo-Saxon countries: raised AST/ALT
    > Francophone countries: hepatic cytolysis
Pieces of a puzzle – Data transformation and analysis

• Transformation:
  – AE case handling (e.g. follow up procedures, coding)

• Analysis:
  – Grouping of similar AE terms (e.g. MedDRA SMQs)
  – Associating AE data with relevant laboratory and vital sign data (e.g. anaemia and haemoglobin)
  – The human body is an interconnected system
    ➢ Problems in one organ system may have an impact on other organ systems (e.g. thrombocytopenia and intracranial haemorrhage)
# Pieces of a puzzle – Examples of strengths and weakness of data used for PV

<table>
<thead>
<tr>
<th>Data set</th>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-clinical</td>
<td>Provides an overall idea of potential risks, informs dose selection</td>
<td>Relevance to patients not always clear</td>
</tr>
<tr>
<td>PK/PD</td>
<td>Informs dose selection and identifies patients at risk (renal/hepatic impairment)</td>
<td>Many ADRs are not dose related</td>
</tr>
<tr>
<td>RCTs</td>
<td>Good quality data, denominator, exposure duration and treatment compliance, concurrent laboratory and vital sign data, can usually detect only common and very common ADRs</td>
<td>Can usually not detect less frequent ADRs, AE reporting may vary between investigators, sites, countries and depend on severity of condition</td>
</tr>
<tr>
<td>Observational</td>
<td>Often have a large sample size, may include long-term data</td>
<td>Bias and confounding</td>
</tr>
<tr>
<td>studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>Only between 1 – 10% of all ADRs are reported, quality reports can be very useful, able to detect less frequent ADRs</td>
<td>No denominator, many poor quality reports, reporting bias, understanding data contributing to data set for EBGM is important</td>
</tr>
<tr>
<td>reports,</td>
<td></td>
<td></td>
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<tr>
<td>EBGM</td>
<td></td>
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<tr>
<td>EHRs</td>
<td>Large cohorts, possibility to combine data from various EHRs, information on prescriptions, indications, may include long-term data</td>
<td>Prescriptions ≠ intake/compliance, biases and confounders not always clear</td>
</tr>
</tbody>
</table>
### Pieces of a puzzle – Causality assessment

<table>
<thead>
<tr>
<th>Bradford-Hill criteria¹</th>
<th>Description</th>
</tr>
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<tr>
<td>Strength</td>
<td>More frequent in exposed vs unexposed</td>
</tr>
<tr>
<td>Consistency</td>
<td>Same observation across various datasets using different methods</td>
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<tr>
<td>Specificity</td>
<td>Known ADR for drug or drug class</td>
</tr>
<tr>
<td>Temporality</td>
<td>Time to onset</td>
</tr>
<tr>
<td>Biological gradient</td>
<td>Dose-response</td>
</tr>
<tr>
<td>Plausibility</td>
<td>Pathomechanism</td>
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<tr>
<td>Experiment</td>
<td>Positive dechallenge/rechallenge, pre-clinical data</td>
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<td>Analogy</td>
<td>Class effect</td>
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<tr>
<td>Coherence</td>
<td>Does all the evidence taken together point in the same direction?</td>
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¹ Bradford-Hill criteria:  

- **Strength**: More frequent in exposed vs unexposed  
- **Consistency**: Same observation across various datasets using different methods  
- **Specificity**: Known ADR for drug or drug class  
- **Temporality**: Time to onset  
- **Biological gradient**: Dose-response  
- **Plausibility**: Pathomechanism  
- **Experiment**: Positive dechallenge/rechallenge, pre-clinical data  
- **Analogy**: Class effect  
- **Coherence**: Does all the evidence taken together point in the same direction?

Beate Aurich. The bottom line of safety data analyses. PSI Conference Amsterdam June 2018.
### Summary of Table 3 - Evidence supporting withdrawal, revocation or suspension of marketing authorisations in the EU since 2012 in Lane et al.²

<table>
<thead>
<tr>
<th>Type of data for 18 drugs</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case reports</td>
<td>17 (94.4%)</td>
</tr>
<tr>
<td>Animal data</td>
<td>13 (72.2%)</td>
</tr>
<tr>
<td>RCTs</td>
<td>13 (72.2%)</td>
</tr>
<tr>
<td>Meta-analysis/Systematic review</td>
<td>13 (72.2%)</td>
</tr>
<tr>
<td>In vitro/ in silico/ ex vivo data</td>
<td>13 (72.2%)</td>
</tr>
<tr>
<td>Non-randomised/ open label</td>
<td>12 (67.7%)</td>
</tr>
<tr>
<td>Cohort studies</td>
<td>10 (55.6%)</td>
</tr>
<tr>
<td>Non-placebo controlled studies</td>
<td>9 (50.0%)</td>
</tr>
<tr>
<td>Observational studies</td>
<td>8 (44.4%)</td>
</tr>
<tr>
<td>Case-control studies</td>
<td>6 (33.3%)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (33.3%)</td>
</tr>
<tr>
<td>Epidemiological studies</td>
<td>4 (22.2%)</td>
</tr>
<tr>
<td>Cross sectional studies</td>
<td>2 (11.1%)</td>
</tr>
</tbody>
</table>
Pieces of a puzzle

- Lane et al.² studied prescription drugs withdrawn, suspended or withheld in Europe (2012-2016)
- Concluding that case reports are "the most commonly used evidence source" by regulators in the EU for these regulatory decisions

Pearls of practice

• The human body is an interconnected system
  ➢ Consider combining signs, symptoms, diagnoses and tests that are related

• Any analysis of safety data should consider
  ➢ What the data/database can & cannot provide
  ➢ Causality assessment of signals

• The bottom line is
  ➢ Causality assessments are an integral part of any PV activity
  ➢ Once safety signals are confirmed as ADRs they will be included into the label/package insert or even lead to a withdrawal of the marketing authorisation
References
