Post marketing surveillance studies in IBD: How meaningful are they and are they prone to bias?

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Safety in the Lifecycle of FDA-regulated Products

Pre-clinical: Safety & Biological Activity

Phase 1: Safety & Dosage

Phase 2: Safety & Efficacy

Phase 3: Safety & Efficacy

Post-Marketing: Safety Surveillance

Safety Concerns

Strategies and Actions to Minimize Risk

“Introduction to Post-marketing Drug Safety Surveillance: Pharmacovigilance in FDA/CDER”
LCDR Monica Muñoz, PharmD, MS, BCPS, Division of Pharmacovigilance, Office of Surveillance and Epidemiology, CDER
February 23, 2016
Goals of post-marketing studies

**Quantify**
- Magnitude of risk
- Background population AE rate
- Compare several treatment alternatives
- Evaluate risk management strategies

**Confirm**
- Rare adverse events
- New drug-drug interactions
  - Long-term risk
- Specific vulnerable/high-risk populations

**Characterize**
- Risk factors
- Risk modifiers
- Time contour
- Drug utilization patterns

Adapted from Wyeth J, Zornberg G. www.fda.gov/downloads/ForPatients/About/UCM410175.pdf accessed on January 8, 2017
Sources of signals

- Observations in patients (qualitative signals)
  - Spontaneous-reporting systems
  - Anecdotal literature reporting
  - Intensive hospital monitoring
  - Prescription event monitoring
  - Follow-up studies
  - Monitored release programs

- Observations in populations (quantitative signals)
  - Large data resources on morbidity and drug use (including record linkage)
  - Case-control studies; case-control surveillance
  - Follow-up studies
  - Prescription event monitoring
  - Intensive hospital monitoring
  - Large spontaneous-reporting systems (e.g. WHO, FDA)

- Experimental findings
  - Clinical trials
  - In vitro experiments
  - Animal toxicology

Types of post-marketing surveillance

• Spontaneous/voluntary reporting of cases
  – National (FDA MedWatch)
  – Local or regional (Joint Commission requirement)
  – Scientific literature publications

• Postmarketing studies (voluntary or required)
  - Observational studies (including automated healthcare databases)
  - Randomized clinical trials

• Active surveillance
  – Drug-Induced Liver Injury Network (DILIN)
  – Sentinel initiative

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Situations favoring signal detection in pharmacovigilance

• Clustering of a clinical event or syndrome with one or more of the following features:
  – a (very) low natural frequency
  – characteristic or unusual (combinations of) signs and symptoms
  – occurring in groups of similar patients (e.g. same age, region, disease history, drug use)
  – known to be frequently drug-induced (e.g. anaphylaxis, agranulocytosis, Stevens-Johnson syndrome)

• High frequency of exposure to the drug

• Adverse effects with one or more of the following features:
  – high frequency
  – suggestive time (immediate reaction, positive rechallenge) or dose relationship
  – plausible pharmacopathological mechanism

Characteristics of Type A events

- Related to the (exaggerated) pharmacological effects of the drug
- Relatively frequent (usually >1 in 100)
- More frequent or severe with higher dosage; may often be avoided by using dosages appropriate for the individual patient
- Time relationship may or may not be suggestive
- May or may not be serious
- Can be studied experimentally (sometimes)
- May be predictable

Examples
- Constipation from narcotics
- Cough induced by ACE inhibitors

Reasons why Type A events may be difficult to detect

- May seem coincidental (e.g., nausea, dizziness)
- Infrequent with low/moderate doses
- No suggestive time relationship
- Occurs in special situations excluded in trials
- Interactions
- Mechanism may be unclear
- Experimental study may be difficult
- Multiple drug use

Suitable methods of detection: clinical trials (phase III and IV), follow-up studies, prescription event monitoring, spontaneous or anecdotal reporting, experimental studies (e.g., in animals).

Characteristics of Type B events

- Often allergic or idiosyncratic reactions (immunological or non-immunological)
- Occur in a minority of patients (often <1 per 1000)
- Pre-existing (often unidentified) predisposing factors
- Usually unexpected and unpredictable; often serious
- Relationship with time and low background frequency often major reasons to suspect the drug
- Mechanism often unknown

Examples
- Hemolytic anemia induced by methyldopa
- Hepatitis induced by isoniazid

Reasons why Type B events may be difficult to detect

- Rare or very rare
- Unexpected, unpredictable
- No suggestive relationship with dosage
- Often no diagnostic test
- May or may not be experimentally reproducible
- Multiple drug use

Suitable methods of detection: spontaneous or anecdotal reporting, prescription event monitoring, case-control studies and case-control surveillance, diagnosis (episode) registrations, large data resources on morbidity and drug use, and record linkage

Characteristics of Type C events

- Increased frequency of ‘spontaneous’ disease
- Occurs at random interval or after long induction time
- Often characteristic, serious, persistent
- Mechanism uncertain
- Drug-induced fraction of the disease may be small

Example
- Relationship of breast cancer and oral contraceptives

Reasons why Type C events may be difficult to detect

• Unexpected, unpredictable
• Often (relatively) high background frequency
• No suggestive time relationship (delayed effects)
• May not be experimentally reproducible
• Multiple causal factors
• Multiple and incomplete drug history
• Absence of adequate comparison (untreated patients)
• High potential for confounding

Suitable methods of detection: case-control studies, long term follow-up studies, large data resources on morbidity and drug use, and record linkage, long interval prescription event monitoring

### Criteria for signal assessment in pharmacovigilance

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Explanation</th>
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</thead>
<tbody>
<tr>
<td><strong>Quantitative</strong></td>
<td></td>
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<tr>
<td>Strength of the association</td>
<td>The number of case reports (in relation to exposure to the drug), statistical disproportionality and significance</td>
</tr>
<tr>
<td><strong>Qualitative</strong></td>
<td></td>
</tr>
<tr>
<td>Consistency of the data</td>
<td>The general presence of a characteristic feature or pattern, and absence or rarity of converse findings</td>
</tr>
<tr>
<td>Exposure-response relationship</td>
<td>Site, timing, dosage-response relationship, reversibility</td>
</tr>
<tr>
<td>Biological plausibility of the hypothesis</td>
<td>Pharmacological and pathological mechanisms</td>
</tr>
<tr>
<td>Experimental findings</td>
<td>Rechallenge, drug-dependent antibodies, high blood or tissue drug concentrations, abnormal metabolites, diagnostic markers</td>
</tr>
<tr>
<td>Analogy</td>
<td>Previous experience with related drugs; event known to frequently be drug-induced</td>
</tr>
<tr>
<td>Nature and quality of the data</td>
<td>Characteristic nature and objectivity of the event, accuracy and validity of documentation, case causality assessment</td>
</tr>
</tbody>
</table>
Statistical power (%) to detect a doubling of adverse event rates in clinical studies of drugs, by sample size

<table>
<thead>
<tr>
<th>Sample size</th>
<th>From 5% to 10%, %</th>
<th>From 1% to 2%, %</th>
<th>From 0.1% to 0.2%, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,000</td>
<td>82</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>5,000</td>
<td>&gt;99</td>
<td>80</td>
<td>7</td>
</tr>
<tr>
<td>10,000</td>
<td>&gt;99</td>
<td>&gt;98</td>
<td>17</td>
</tr>
<tr>
<td>50,000</td>
<td>&gt;99</td>
<td>&gt;99</td>
<td>79</td>
</tr>
</tbody>
</table>

### Suitable methods for detecting adverse drug effects, according to the frequency of the adverse effects

<table>
<thead>
<tr>
<th>Detection Method</th>
<th>Frequency of adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;1/10</td>
</tr>
<tr>
<td>Spontaneous reporting (national)</td>
<td>-</td>
</tr>
<tr>
<td>International reporting</td>
<td>-</td>
</tr>
<tr>
<td>Intensive monitoring</td>
<td>-</td>
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<tr>
<td>Prescription event monitoring</td>
<td>-</td>
</tr>
<tr>
<td>Case-control surveillance</td>
<td>-</td>
</tr>
<tr>
<td>Large data resources and record linkage</td>
<td>-</td>
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<tr>
<td>Follow-up studies</td>
<td>-</td>
</tr>
<tr>
<td>Monitored release</td>
<td>-</td>
</tr>
<tr>
<td>Clinical trials</td>
<td>++</td>
</tr>
</tbody>
</table>

Some post-marketing surveillance studies in IBD

- TREAT: infliximab in Crohn’s disease (US)
- ENCORE: infliximab in IBD (Europe)
- PYRAMID: adalimumab in Crohn’s disease
- SECURE: certolizumab pegol in Crohn’s disease
- TOUCH: natalizumab in Crohn’s disease
Publications from post-marketing surveillance studies in IBD


TREAT Registry: Infliximab in Crohn’s disease

- Prospective, observational, multicenter, long-term registry of North American patients with CD initiated in 1999 to evaluate the safety outcomes
- ~350 gastroenterologists from community-based (~80%) and academic practice (~20%) settings were each to enroll up to 150 patients; target enrollment of at least 5,000
- Subjects managed at discretion of their physicians (i.e., no pre-defined treatment protocol)
- Data collected on a semi-annual basis (January and July of each year) and followed at least 5 yr
- Physicians assessed disease severity as per ACG as remission, mild-moderate, moderate-severe, or severe-fulminant
- Data collected: disease severity, medication use, adverse events, dates and outcomes of each infliximab infusion (infusion reaction: yes/no)
- Specific adverse events, including infusion reactions, infections, and malignancies

Flow of participation in TREAT Registry

TREAT: What did we learn?

• Crude cancer incidences similar between patients receiving infliximab and other-treatments-only

• Age, disease duration, and smoking each independently associated with malignancy risk but immunosuppressant and/or infliximab use were not

• Relative to the general population, no significant increase in incidence observed in any malignancy category

• In exposure-based analysis, use of immunosuppressants alone or in combination with infliximab seemed to be associated with a numerically, but not significantly, greater risk of malignancy than did treatment with infliximab alone relative to treatment with neither

Vedolizumab Post-Marketing Commitment under FDAAA Section 505(o)(3)

A postmarketing, prospective, observational, cohort study of VDZ vs. other agents for IBD

Primary outcome
• Serious infections

Secondary outcomes
• PML
• Malignancy
• Specific infections including gastrointestinal and upper respiratory infections

“Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in serious infection risk above the comparator background rate, with a pre-specified statistical analysis method”

“Ensure adequate number of patients with at least 24 months of vedolizumab exposure at the end of the study.”

http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm
Are post-marketing studies in IBD biased?

- Yes....but in what ways?
  - Patient selection?
  - Differential follow up of outcomes?
  - Ascertainment of exposures?
  - Ascertainment of confounding risk factors?
Assessing Causality

Drug \rightarrow \text{Adverse Effect}

\text{Direct}

\text{Indirect}

\text{Confounder}

\text{Disease Severity}
\text{Other Drug}

\text{Chance}
\text{Unsystematic variation}

\text{Bias}
\text{Systematic variation}
What is a drug’s safety risk?

“The stones are placed so that the entire composition cannot be seen at once from the veranda. They are also arranged so that when looking at the garden from any angle (other than from above) only fourteen of the boulders are visible at one time. It is traditionally said that only through attaining enlightenment would one be able to view the fifteenth boulder.”

Ryōan-ji, Kyoto, Japan

Concept of Wyeth & Zornberg

https://en.wikipedia.org/wiki/Ry%C5%8Dan-ji accessed on January 8, 2017