Postmarket Drug Safety Surveillance: Cardiovascular Toxicities

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Center for Drug Evaluation and Research
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Outline

• Definition and Utility of Pharmacovigilance
• FDA Adverse Event Reporting System (FAERS) and Data Mining
• Case Series Development and Evaluation
• Postmarket Safety Analysis: Everolimus-Associated Cardiac Failure
• Postmarket Safety Analysis: Cardiovascular Toxicities Associated with Immune Checkpoint Inhibitors
Pharmacovigilance

The science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems.

* The Importance of Pharmacovigilance, World Health Organization 2002
# Pharmacovigilance

## Limitations of Premarket Clinical Trials

- Relatively small size of patient population
- Narrow population - often not providing sufficient data on special groups
- Narrow indications studied
- Short duration

## Benefits of Postmarket Monitoring -

*Ability to study the following:*

- Low frequency reactions (not identified in clinical trials)
- High-risk groups
- Long-term effects
- Drug-drug/food interactions
- $\uparrow$ Severity and/or reporting frequency of known reactions
FDA Adverse Event Reporting System

- A computerized database of spontaneous reports
- Contains human drug and therapeutic biologic reports
- ~13 million reports since 1968
- Over 1.69 million new reports in 2016
FDA Sources of Postmarket Reports

Patients, consumer, and healthcare professionals

Voluntary

FDA MedWatch

Manufacturer

Voluntary

Regulatory Requirements

FDA

5% of all reports

95% of all reports

FAERS Database
Adverse Event Reports Entered into FAERS

Number of Adverse Event Reports

Year

Number of Reports

- Non 2015
- Non-Expedited
- 15-Day
- Direct
Sources of Possible Safety Signals

1. FAERS
2. Data Mining
Use of Data Mining

- Mathematical tool identifies higher-than-expected frequency of product-event combinations
- Tool for hypothesis generation
- Supplements FAERS data review
- Does not replace expert clinical case review
Case Series Development and Evaluation
Developing a Case Series

- Identify a potential safety signal
- Complete broad FAERS/literature search
- Formulate case definition based on clinical diagnosis of event
- Apply case definition for case series development
- Evaluate case for presence of drug-event association
**Principles of Case Evaluation**

- **Causality assessment**: World Health Organization, the Uppsala Monitoring Centre (WHO-UMC):
  - Certain
  - Probable/Likely
  - Possible
  - Unlikely
  - Conditional/Unclassified

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**Temporal relationship**

**Key factors in causality assessment**

- **Biologic plausibility**
- **Pre/post-event clinical work-up**
- **Concomitant medications/comorbidities**
- **Positive dechallenge/rechallenge**
Possible Review Outcomes

Regulatory Actions

- Enhanced Surveillance
- Risk Evaluation and Mitigation Strategy (REMS)
- Market Withdrawal

Methods of communication may include:

1. Drug Safety Communication
2. Publication in a peer-reviewed journal
Safety Signal Review: Everolimus and Cardiac Failure
Identify a potential safety signal

Numerous reports of cardiac failure in FAERS and published medical literature

Complete broad FAERS/literature search

Used 12 MedDRA preferred terms to identify over 300 reports

Formulate case definition based on clinical diagnosis of event

Case definition adopted from Cardiac Review and Evaluation Committee for trastuzumab clinical trials

Apply case definition for case series development

Case series consisted of 148 FAERS and literature cases

Evaluate case for presence of drug-event association

Postmarket Safety Signal: Everolimus and Cardiac Failure

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Evaluate case for presence of drug-event association
### Key Findings in Determining Drug-Event Association

<table>
<thead>
<tr>
<th>Category</th>
<th>Characteristic</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Top 3 Indications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td></td>
<td>65</td>
</tr>
<tr>
<td>Breast cancer</td>
<td></td>
<td>47</td>
</tr>
<tr>
<td>Pancreatic neuroendocrine tumor</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td><strong>Risk factors (RF) for cardiac failure</strong></td>
<td>Concomitant/prior meds labeled for cardiac failure and LV dysfunction</td>
<td>63</td>
</tr>
<tr>
<td>Cardiac RF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 RF</td>
<td></td>
<td>46</td>
</tr>
<tr>
<td>2 RF</td>
<td></td>
<td>33</td>
</tr>
<tr>
<td>3 RF</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>&gt;4 RF</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>No RF</td>
<td></td>
<td>31</td>
</tr>
<tr>
<td>None reported</td>
<td></td>
<td>26</td>
</tr>
<tr>
<td><strong>Time to Onset</strong></td>
<td>Median days to onset (range)</td>
<td>86 (3-1143)</td>
</tr>
<tr>
<td>Time to onset ≤ 90 days</td>
<td></td>
<td>75</td>
</tr>
<tr>
<td><strong>Rechallenge information</strong></td>
<td>Positive rechallenge</td>
<td>2</td>
</tr>
<tr>
<td><strong>Severity</strong></td>
<td>Fatal outcome reported</td>
<td>43</td>
</tr>
<tr>
<td>Heart failure as cause of death</td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>Reported Grade 3/4 decrease in LVEF</td>
<td></td>
<td>30</td>
</tr>
</tbody>
</table>
Regulatory Action: Labeling Revision

• Discussed findings with Office of New Drugs (OND) designated Review Division

• Decision made to include under **Adverse Reactions – Postmarketing Experience** in the product information

• Peer reviewed medical journal: [J Clin Oncol 34, 2016 (supple;a bstr e18226)](http://example.com)
Cardiovascular Toxicities Associated with Immune Checkpoint Inhibitors in the Postmarket Setting
Cardiovascular Toxicity in Immune Checkpoint Inhibitor Product Information

<table>
<thead>
<tr>
<th>Checkpoint Target</th>
<th>Product</th>
<th>Labeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTLA-4</td>
<td>Ipilimumab</td>
<td><strong>Warnings and Precautions: Other immune-mediated adverse reactions</strong>&lt;br&gt;• Pericarditis, fatal myocarditis&lt;br&gt;<strong>Adverse Reactions: Clinical trials experience</strong>&lt;br&gt;• Pericarditis (including fatal outcome), myocarditis (including fatal outcome)</td>
</tr>
<tr>
<td>PD-1</td>
<td>Nivolumab</td>
<td><strong>Dosage and Administration: Dose modifications</strong>&lt;br&gt;• Grade 3 myocarditis – permanently discontinue&lt;br&gt;<strong>Warnings and Precautions: Other immune-mediated adverse reactions</strong>&lt;br&gt;• Myocarditis&lt;br&gt;<strong>Adverse Reactions: Clinical trials experience</strong>&lt;br&gt;• Cardiac disorders: ventricular arrhythmia</td>
</tr>
<tr>
<td>PD-1</td>
<td>Pembrolizumab</td>
<td><strong>Warnings and Precautions: Other immune-mediated adverse reactions</strong>&lt;br&gt;• Myocarditis&lt;br&gt;<strong>Adverse Reactions: Clinical trials experience</strong>&lt;br&gt;• Cardiac failure (0.4%)&lt;br&gt;• Myocarditis (0.5%)&lt;br&gt;<strong>Medication Guide</strong>&lt;br&gt;• Shortness of breath, irregular heartbeat, feeling tired, or chest pain (myocarditis)</td>
</tr>
</tbody>
</table>
# Cardiovascular Toxicity in Immune Checkpoint Inhibitor Product Information

<table>
<thead>
<tr>
<th>Checkpoint target</th>
<th>Product</th>
<th>Labeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1</td>
<td>Avelumab</td>
<td><strong>Dosage and Administration: Dose modifications</strong>&lt;br&gt;• Other immune-mediated adverse reactions: Myocarditis – either withhold or discontinue based on severity immune-mediated adverse reactions&lt;br&gt;<strong>Warnings and Precautions: Other immune-mediated adverse reactions</strong>&lt;br&gt;• Immune-mediated myocarditis including fatal cases</td>
</tr>
<tr>
<td></td>
<td>Durvalumab</td>
<td><strong>Warnings and Precautions: Other immune-mediated adverse reactions</strong>&lt;br&gt;• Myocarditis&lt;br&gt;<strong>Patient Counseling Information</strong>&lt;br&gt;• Myocarditis</td>
</tr>
<tr>
<td></td>
<td>Atezolizumab</td>
<td><strong>Adverse Reactions: Clinical trials experience</strong>&lt;br&gt;• Myocardial infarction</td>
</tr>
</tbody>
</table>
Notable Postmarket Literature Publications of Myocarditis

**Johnson et al. NEJM. 2016.**

- Fatal fulminant myocarditis in 2 patients treated with combination ipilimumab and nivolumab
- **Supportive evidence for a drug-event association:**
  - Temporal association
  - Laboratory information provided (i.e. CK-MB, troponin)
  - Viral studies
  - Lymphocytic infiltration within the myocardium and skeletal muscle
  - PD-L1 was expressed on injured myocytes and on infiltrating lymphocytes

**Heinzerling et al. Journal for Immunotherapy of Cancer. 2016.**

- Case series of 8 patients cardiotoxicity following immune checkpoint treatment
- 4 of 8 cases were myocarditis
- **2 fatal cases**
- **Supportive evidence for a drug-event association:**
  - Temporal relationship
  - Reduced ejection fraction from baseline
  - Cardiac biopsy determined lymphocyte-induced infiltration
  - Endomyocardial biopsy
  - Viral studies
Atezolizumab and Myocarditis

• Atezolizumab product information does not include risk of myocarditis

• Identified reports of myocarditis in FAERS and the medical literature

• Sufficient data to initiate review

• Genentech issued Dear Health Care Provider Letter
  – Includes analysis of company safety data in the postmarket setting
  – Prescriber action recommendation
Postmarket Literature Reports of Other Cardiovascular Toxicities

- Acute pulmonary edema
- Cardiac arrest
- Cardiac failure (acute, congestive)
- Cardiac tamponade
- Cardiopulmonary failure
- Cardiorespiratory arrest
- Hypertension
- Left bundle branch block
- Left ventricular dysfunction
- Myocardial infarction
- Myocardial fibrosis
- Paroxysmal atrial fibrillation
- Pericardial effusion
- Pericarditis
- Pulmonary edema
- Subacute Takotsubo-like cardiomyopathy
- Transient supraventricular tachycardia
- Ventricular arrhythmia

Potential safety signals that require further analysis
Challenges of Evaluating Postmarket Reports of Other Cardiovascular Toxicities

• Differentiating other cardiovascular adverse events from the spectrum of myocarditis

• Reported cardiovascular adverse events have a high background rate in the general population

• Potential contributory role of comorbidities or concomitant medications

• Variable quality of reporting
Future Directions

• Continued pharmacovigilance monitoring of immune-mediated and non-immune mediated cardiovascular toxicities with immune checkpoint inhibitors

• Collaborative work with subject matter experts: cardiologists, oncologists, Board Certified Oncology Pharmacists (BCOP) in DPV

• Determine optimal language in the product information to convey risk to health care practitioners

• Consider the impact of postmarket data on guiding clinical practice on the monitoring and management of cardiovascular toxicities with immune checkpoint inhibitors
Reporting to MedWatch

• How to Report:
  – Online
    (www.fda.gov/medwatch)
  – Download the form
  • Mail
  • Fax 1–800–332–0178
  • For questions about the form:
    1–800–332–1088
Back-Up Slide
Panel Discussion Questions

1. What is the best strategy to identify and characterize other cardiovascular toxicities with immune checkpoint inhibitors in the postmarket setting?

2. How do we differentiate cardiovascular toxicities that result from immune checkpoint inhibitor-induced myocarditis versus a non-immune-mediated mechanism?

3. What is the clinical threshold for including specific language for cardiac monitoring in the product information of immune checkpoint inhibitors?