Post-market drug safety measures in Japan
-Regulatory Experiences on Utilization of Electronic Medical Records-

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Importance of post-market safety assessment

Limitations at the time of approval: Five “too”es
- too few
- too simple
- too median-age
- too narrow
- too brief

Rapid expansion of number of patients taking a drug with various backgrounds
- Unexpected ADR may occur
- Continuous safety assessments and proper safety measures are the key to minimizing a risk and assuring benefit/risk balance of drugs

(A.S. Rogers, Drug Intelligence and Clinical Pharmacy, 21, 1987)
Overview of the regulatory schemes of pharmacovigilance in Japan

EPPV : Early Post-marketing Phase Vigilance (6 months intensive monitoring)
RMP  : Risk Management Plan
Re-EX : Re-examination
Re-EVA: Re-evaluation
Data processing flow of safety reports

HCPs
- E-mail
- Fax
- Post

via

Create ICSR files by PMDA

Patients
via
- Website

MAHs
via
- Electrical transmission
- Post
- Over-the-counter
*Submission of ICSR files is mandatory

Populate into ADR DB

Drugs

Medical Devices

Populate ICSR into ADR DB

PMDA

Data Analysis
Changes in the numbers of reports on adverse drug reactions/infections

<table>
<thead>
<tr>
<th>Year</th>
<th>from MAH (Japanese case)</th>
<th>from MAH (Foreign case)</th>
<th>from HCP</th>
</tr>
</thead>
<tbody>
<tr>
<td>FY 2012</td>
<td>41,413</td>
<td>261,862</td>
<td>0</td>
</tr>
<tr>
<td>FY 2013</td>
<td>38,427</td>
<td>266,539</td>
<td>4,147</td>
</tr>
<tr>
<td>FY 2014</td>
<td>5,420</td>
<td>300,216</td>
<td>5,402</td>
</tr>
<tr>
<td>FY 2015</td>
<td>6,180</td>
<td>345,193</td>
<td>6,129</td>
</tr>
<tr>
<td>FY 2016</td>
<td>6047</td>
<td>55,817</td>
<td>6047</td>
</tr>
</tbody>
</table>

Annual report FY2016
Various levels of safety measures

**Decision of safety measures**

- withdrawal of approval
- revision of precautions for use of package insert etc.

**Provision of safety information to MAHs, HCPs and the public**

**Yellow Letter**
(Dear Healthcare Professional Letters of Emergent Safety Communications)

**Blue Letter**
(Dear Healthcare Professional Letters of Rapid Safety Communications)

**PMDSI** (Pharmaceuticals and medical devices safety information)

Notification of instruction to revise the “precaution for use” section of the package insert
Regulatory decisions on safety measures have been mainly based on spontaneous adverse reports.

Example of safety measures

<table>
<thead>
<tr>
<th>Date</th>
<th>Situation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013. 12. 6</td>
<td>Simeprevir was approved for hepatitis C virus (HCV) genotype 1 of chronic HCV infection</td>
</tr>
<tr>
<td>Up to 2014.10.10</td>
<td>8 serious cases of hyperbilirubinemia including 3 death cases were reported</td>
</tr>
<tr>
<td></td>
<td>Review cases in PMDA</td>
</tr>
<tr>
<td>2014. 10. 24</td>
<td>Warning letter (Blue letter: Dear Healthcare professions letter)</td>
</tr>
<tr>
<td></td>
<td>• Routine monitoring of bilirubin in the blood</td>
</tr>
<tr>
<td></td>
<td>• More cautions on jaundice etc.</td>
</tr>
</tbody>
</table>
Limitations of traditional process

- Reporting Bias: Under-reporting of adverse drug reactions
- Limitation in quantitative analysis:
  - Lack of adequate denominator information
- No control group: Most of post-marketing studies have conducted as single-arm studies
  - Not easy to distinguish adverse drug reactions from events associated with underlying diseases or other factors

<Challenges>

Additional data sources such as a real world data should be available in addition to the traditional sources for more scientific and quantitative approaches on drug safety assessment
MIHARI project
(Medical Information for Risk Assessment Initiative)

Conventional Information Sources
- Spontaneous ADR report DB
- Literatures
- Overseas regulatory actions
- Presentation in Academic Conference

Electronic Healthcare Data
- Claims DB
- MID-NET (EMR DB)
- DPC DB

Launched in 2009

PMDA

MHLW

Medical institutions

Safety measure
Risk communication

Literatures
Overseas regulatory actions
Presentation in Academic Conference

etc
Role of Pharmacoepidemiologist

- In pre-approval
  - Review Risk Management Plan
  - Propose appropriate post-marketing studies etc.
- In post-approval
  - Conduct PEpi studies utilizing EMRs database for drug safety assessment
  - Review PEpi data/reports submitted by industries etc.
MIHARI
-Example-
Oseltamivir & Abnormal Behavior

- Serious cases of abnormal behaviors in Japanese teenagers after taking Oseltamivir were reported in 2006-2007 flu season.
- MHLW issued “Dear Healthcare Professional Letter” for not using Oseltamivir in teenagers patients in March 2007
- Claim data were utilized to examine effects of the regulatory actions on anti-influenza drug use in Japan.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Date</th>
<th>Regulatory Actions</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oseltamivir</td>
<td>Mar 2007</td>
<td>“Dear Healthcare Professional Letter” for creating a boxed warning</td>
<td>Conveying physicians not using Oseltamivir in patients of 10-19 years of age in principle</td>
</tr>
</tbody>
</table>
Prescription of Oseltamivir in Japan

Results based on analysis of claim database
(Total number of subjects in the database = 399,086)

<table>
<thead>
<tr>
<th>Flu season</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>19,296</td>
</tr>
<tr>
<td>female</td>
<td>16,554</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>0-9</td>
<td>13,384</td>
</tr>
<tr>
<td>10-19</td>
<td>5,538</td>
</tr>
<tr>
<td>≥20</td>
<td>16,928</td>
</tr>
<tr>
<td>Total</td>
<td>35,850</td>
</tr>
<tr>
<td>Mean ± SD (years)</td>
<td>22 ± 17</td>
</tr>
<tr>
<td>Mid (years)</td>
<td>15</td>
</tr>
</tbody>
</table>
Impacts of regulatory action (anti-Influenza drug)

Monthly trends of teen-age patients (10-19 years of age) who were prescribed anti-influenza drugs from 2005 to 2008

Confirmed the significant change on oseltamivir prescription pattern to teen-age patients after the regulatory action.
Risk evaluation of Atypical Antipsychotics (AAP) for Hyperlipidemia: A Sequence Symmetry Analysis


Number of days since an initial administration of AAP
Risk of Acute Asthma Attacks Associated With NSAIDs: A Self-Controlled Case Series.

Definition of acute asthma attacks: the combination of an inhalation procedure and the prescription of any inhaled β2-agonist.

Risk of Acute Asthma Attacks Associated With NSAIDs: A Self-Controlled Case Series

Table 2. Characteristics of the Study Population Who Had Been Prescribed NSAIDs and Had Experienced an Acute Asthma Attack (N = 9769 Patients).

<table>
<thead>
<tr>
<th>Gender</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>4562</td>
<td>46.7</td>
</tr>
<tr>
<td>Women</td>
<td>5207</td>
<td>53.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age range, y</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9</td>
<td>1082</td>
<td>11.1</td>
</tr>
<tr>
<td>10-19</td>
<td>1583</td>
<td>16.2</td>
</tr>
<tr>
<td>20-29</td>
<td>1530</td>
<td>15.7</td>
</tr>
<tr>
<td>30-39</td>
<td>2663</td>
<td>27.3</td>
</tr>
<tr>
<td>40-49</td>
<td>1837</td>
<td>18.8</td>
</tr>
<tr>
<td>50-59</td>
<td>783</td>
<td>8.0</td>
</tr>
<tr>
<td>60-69</td>
<td>259</td>
<td>2.7</td>
</tr>
<tr>
<td>≥70</td>
<td>32</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

*At the start of each patient’s observation period.

Incident Rate Ratio

MID–NET® Project
–More details, More timely–
The Medical Information Database Network in Japan for a real-time assessment of drug safety (currently 4M patients).

An integrated real time EMRs database with high quality
Data categories in the MID-NET® system

- Database
  - HIS data
  - Claims data
  - DPC data

Example of standard code

<table>
<thead>
<tr>
<th>Contents</th>
<th>Standard</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease</td>
<td>ICD-10</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>YJcode, HOT9</td>
<td></td>
</tr>
<tr>
<td>Laboratory test</td>
<td>JLAC10</td>
<td></td>
</tr>
<tr>
<td>Bacteriological test</td>
<td>JANIS</td>
<td></td>
</tr>
</tbody>
</table>

HIS data

- Patient identifying data
- Medical examination history data (including admission, discharge data)
- Disease order data
- Discharge summary data
- Prescription order/compiled data
- Injection order/compiled data
- Laboratory test data
- Radiographic inspection data
- Physiological laboratory data
- Therapeutic drug monitoring data
- Bacteriological test data
Data integration method of MID-NET

Onsite Center

User

① Create program

② Request for running program

Technical staff for MID-NET

③ Approve the request

④ Output

Hospitals

Original databases

- Medical record
- Labo test data
- Claims
- Others

Standardization

Anonymization

Common data model database for MID-NET

Central data center

⑤ Approve to send data

⑥ Send data

⑦ View & Analysis

⑧ Output

User

① Create program

② Request for running program

③ Approve the request

④ Output

Technical staff for MID-NET

① Create program

② Request for running program

③ Approve the request

④ Output
PMDA has worked with cooperative hospitals for assuring data quality of MID-NET®.
Develop SAS programs for typical epidemiological studies

Target study design for the library

**Drug utilization study**
- Volume of prescriptions, days of prescriptions and interval of prescriptions (to use other programs)

**Cohort study**
- Single Cohort (Investigation of event occurrence and patient background)
- Double Cohort (Adjust covariates and investigate the relationship between risks and exposures)

**Nested case control**
- Focusing on a specific outcome, investigate the risk by the presence or absence of risk factors

**Interrupted time series**
- Investigate transitions before and after safety measures to evaluate impacts of the measures
A pilot study of MID-NET®
<Background>

- In EU/US, codeine is contraindicated in patients under 12 years due to the higher risk of respiratory depression induced by this drug. Regulatory action in US was taken in April 2017.
- In Japan, prescription of codeine-containing products to patients under 12 years should be made with careful consideration but no contraindication is mentioned.
- Lower prevalence of ultra-rapid metabolizer of codeine in Japanese than Caucasian.

<Study Objective>
Evaluate drug utilization and risk of respiratory depression of codeine-containing product in Japanese patients.
MID-NET® pilot: Case 1
Codeine and respiratory depression

■ Methods: Drug Utilization Study

Source Population

Patients visited cooperative
N = 976,859 *

Exclude
- Not using codeine-containing product
- Diagnosed cancer before prescribing codeine-containing product

Cohort

Patients using Codeine-containing Product
N = 7,267

Subgroup 1
Age below 12 years*
N = 209

Subgroup 2
Age between 12 and 18*
N = 199

Subgroup 3
Age above 18 years*
N = 6,859

*: 7 medical institutions

*: Age at first prescription
Possible cases causing respiratory depression during prescription of codeine-containing product

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Number of cases</th>
<th>Population</th>
<th>Incidence Proportion(%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subgroup 1 : &lt; 12 years old*</td>
<td>Masked*¹</td>
<td>209</td>
<td>Masked*¹</td>
<td>0.0-1.0</td>
</tr>
<tr>
<td>Subgroup 2 : 12-18 years old*</td>
<td>0</td>
<td>199</td>
<td>0</td>
<td>0.0-0.0</td>
</tr>
<tr>
<td>Subgroup 3 : &gt; 18 years old*</td>
<td>Masked*¹</td>
<td>6,859</td>
<td>Masked*¹</td>
<td>0.2-0.5</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>7,267</td>
<td>0.3</td>
<td>0.2-0.4</td>
</tr>
</tbody>
</table>

- Suspected cases of respiratory depression were confirmed by definition 1 or 2.
  - Definition 1 : Prescription of drugs*²
  - Definition 2 : Related disorders*³ of respiratory depression and treatments of oxygen inhalation

*¹ When the number of cases in the subgroup is less than 10 people, concrete numerical values are not disclosed from the viewpoint of protection of personal information
*² Prescription of drugs : levallorphan or naloxone
*³ Related disorders : respiratory distress, acute respiratory failure or respiratory failure

MHLW recently notified to change a Japanese label of codeine-containing products to follow the warning status in EU/US
Hypocalcemia was identified as one of important risk at the time of approval

- The label included warning and descriptions of risk management for hypocalcemia

- However, serious adverse events including death cases have been reported at post-market in Japan and overseas
Warning letter was issued on September 12th 2012

A) More laboratory test on serum calcium etc.
B) Co-administration of calcium/vitamin D
C) Special caution to patients with severe impairment of renal function
D) Prepare for emergency situation

<Study Objective>
What is the impact of the warning letter in clinical practice?
MID-NET® pilot: Case 2
denosumab and severe hypocalcemia

Methods: Interrupted time series

MID-NET®
6 medical institutions
(Jan. 2010 – Mar. 2014)

Patients using denosumab or zoledronate from

Denosumab
Before the measure
N=104
After the measure
N=563

Intervals before the measure
Intervals after the measure

Zoledronate
Before the measure
N=665
After the measure
N=1,055

Control Group

• Calculate the incidence of hypocalcemia during 28 days from a prescription date.
• Perform segment regression analysis based on the incidence of hypocalcemia / month.
MID-NET® pilot: Case 2
denosumab and severe hypocalcemia

Monthly transition of the incidence of hypocalcemia

- Although the risk of hypocalcemia during denosumab prescription was high just after approval, but gradually decreased over time.
- The warning letter (blue letter) may contribute to maintaining the risk at lower level, while it has no proven impacts in decreasing the risk ratio.
<Study objective>
Can risk of liver dysfunction associated with a new drug be actively and continuously monitored in MID-NET®
MID-NET® pilot: Case 3
Amiodarone & Nifekalant on risks of liver dysfunction

Entry Criteria
- Prescription of target drugs in the study period
- Records for at least 180 days before the first prescription

Exclusion Criteria
- Record of abnormality on liver function test at the period of 180 days before the first prescription
- Concurrent prescription of the targeted two drugs at the first prescription

Cohort

Amiodarone (n=142)
Nifekalant (n=114)

1:1 matching
Gender, age(±10), t₀(±180 days)

Matched population

Amiodarone (n=88)
Nifekalant (n=88)
Definition of Liver dysfunction:
- at least 5 times higher than maximum threshold of normal range on laboratory test of ALT, AST or ALP

- Similar trend was also confirmed in the matched populations
Recent activities
-Patients Registries-
Patients registries and Challenges

- Current patient registries mainly focus on academic research for grasping patient backgrounds in clinical practice
  - A lack of items for regulatory review
  - Less interventional data (e.g.: prescription date, drug name, dose, prescription period etc.)
  - Less standardized data
  - Non-coded data
  - A lack of quality management
  - Small sample size

A patient registry which can be utilized for post-marketing study of a new drug and/or for drug development

Establishment of Clinical Innovation Network (CIN)
Clinical Innovation Network and PMDA

MHLW

PMDA CIN-Working Group

AMED

Advice, Cooperation

About 20 members from New drugs & Safety Offices

Muscular dystrophy Registry
by NCNP

ALS (Antilymphocytic serum) Registry
By Nagoya Univ.

Cancer registry
By National Cancer Center Japan

Cerebral surgery
By Japan neurosurgical society

Study group for epidemiological methods and data quality standards

Study group for ethical issues for registries and relationships with industries

Output

Utilizing registry data for promoting cost effective clinical studies, accelerating drug development, and extending healthy life expectancy
PMDA Regulatory Science Center
Utilization of e-data for better regulatory decision in
- Development
- Pre-Approval
- Pharmacovigilance

“BIG DATA”-utilized Assessment & Regulation

Archives of e-data
- EMR Data
- CDISC Data

Active Utilization

Better Prediction
Better B/R balance
More Successful Development
Active utilization of EHR databases toward advanced medical care

**Regulatory decisions based on better scientific evidences**
- Proper safety assessment utilizing HER databases in addition to the traditional approaches

**RMP implementation utilizing EHR databases**
- Efficient risk management
- Better quality of safety information

**Provide leading-edge Medical Therapy with ensuring Safety**
- Scientific and speedy safety measure

**Better quality of Medical Care**
- Maximize benefit/risk ratio
PMDA web site

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