Utilization for Real-World Data on Post Marketing Drug Safety assessment in PMDA

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Japan
1. More scientific contributions during development through consultation

2. Utilizing “BIG DATA” for improving quality of approval review and safety assessment

3. Promoting regulatory science
   - Developing methods and criteria for responding to advances in science and more

Nature Reviews Drug Discovery 13, 490 (2014)
Today’s Agenda

• Limitation of traditional process of the post-marketing drug safety assessment
• MIHARI Project
• MID-NET Project
• Point to consider in utilizing EMRs for drug evaluation
• Future perspectives
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Traditional process of drug safety measures in Japan

Drug safety assessment using the conventional data sources

- Spontaneous ADR report DB
- Literatures
- Overseas regulatory actions
- Presentation in Academic Conference
  etc

MHLW: Ministry of Health, Labour and Welfare, Japan
Limitations of traditional process

• Under-reporting of ADR (Reporting biases)
• Lack of adequate denominator information of drug utilization for estimation of risk
• Not available of the comparative incidence rates between drugs in post-marketing studies that had no comparison group
• Sometimes difficult to distinguish ADR from events associated with underlying diseases or other factors

Other source of information and other methods are required
– To strengthen post-marketing drug safety measures and compensate for the limitations
PMDA’s challenges

• Two projects to reinforce and enhance post-marketing drug safety measures in PMDA
  ➢ **MIHARI Project**  (MIHARI means “monitor” in Japanese)
    Establishment of a framework in PMDA to utilize Pharmacoepidemiological methods for safety assessment of a drug
  ➢ **MID-NET Project**  (Medical Information Database NETwork)
    Establishment of a new medical information database in Japanese patients for safety assessment of a drug
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• MID-NET Project

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• Future perspectives
MIHARI Project

Medical Information for Risk Assessment Initiative
Goal of MIHARI Project

Drug safety assessment using the conventional information sources:
- Spontaneous ADR report DB
- Overseas regulatory actions
- Literature
- Presentation in Academic Conference
- etc.

Drug safety assessment using the electronic healthcare data:
- Claims DB
- MID-NET (EMR DB)
- DPC DB
- etc.

PMDA

MHLW

Medical institutions

Safety measure

Risk communication
Methods & Applications in Pharmacovigilance

Signal Detection
- **Data Mining**
  Detect primary signals from all pairs of drugs and events by data mining method.

Signal Refinement
- **Drug utilization study**
  Survey for patient background or prescription trend in a specific population defined by diagnosis or drug
- **Evaluation of effects of regulatory actions**
  Survey for prescription trend or compliance of cautions after a regulatory action is taken

Alert detection
- Secondary signal detection of specific combination of event and drug by pharmacoepidemiological methods

Signal Evaluation
- **Causal Effect Measurement**
  Estimate association of specific pair of drug and event by pharmacoepidemiological method.
- **Case Validation study**
  Validate some case definitions for database study by medical chart review.
MIHARI’s Investigative Approach in the pilot phase

Ensuring Access to Electronic Health Record Data
- Data collection scheme
- Data cleaning method

Data Characterization
- Data validation
- Data limitation

Data Utilization
- Epidemiological studies
- Interpretation of study results
MIHARI’s Investigative Approach in the pilot phase

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Data Utilization
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Current data sources available in Japan (1)

- **Claims data**
  - The data for the purposes of reimbursement
  - Data in the standardized format is created
    - Claims data from health insurance associations
      - About 2 million patients
      - Commercially available
    - National Claims data from government
      - Almost all of patients in Japan (over 127 million patients)
      - Applicants approved through a rigorous review can use

- **Diagnosis and Procedure Combination (DPC) data**
  - Prospective payment system for acute inpatient medical care
  - Data in the standardized format is available
    - Holders of databases perform all analysis in response to requests
Current data sources available in Japan (2)

**Electrical Medical Record (EMR)**
- EMR includes detailed information on medical practices within medical institution
  - EMR includes data from HIS (Hospital Information System)
  - One is the key feature is that the data includes the laboratory test results
- HIS data is created by customized system according to each hospital’s need
  - HIS data needs to be transformed into a standardized format
- EMR available in Japan
  - MID-NET (described below)
  - Some researchers may use the standardized EMR by collaborating with some medical institutions
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- Data validation
- Data limitation

Data Utilization
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Pilot studies in the pilot phase (2009-2013)

• More than 40 pilot studies were conducted
  ➢ To assess the feasibility of applying the well-known pharmacoepidemiological design/methods to drug safety assessment with Japanese electronic healthcare data
  ➢ In pilot studies, already well-known safety issues were evaluated
The design/methods used

• Design
  – Cohort design
  – Nested case control design
  – Sequence Symmetry Analysis
  – Self-controlled case series
  – Validation study

• Methods
  – Segment regression analysis
  – Propensity score (PS) methods for control confounding
Example: Impacts of regulatory action (anti-Influenza drug)

Objectives:
To assess impacts of regulatory safety measure for an individual products using the Japanese claims data
Example: Risk of acute asthma attack associated with NSAIDs: A Self-Controlled Case Series (1)

- **R0** = 7 days before prescription start date
- **R1** = the prescription start date
- **R2** = 1–9 days after the prescription start date
- **R3** = > 9 days after the prescription start date
- **R4** = 7 days after the prescription end date

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

Example: Risk of acute asthma attack associated with NSAIDs: A Self-Controlled Case Series (2)

| Characteristics of the Study Population Who Had Been Prescribed NSAIDs and Had Experienced an Acute Asthma Attack (N = 9769 Patients) |
|---|---|
| Gender | N | % |
| Men | 4562 | 46.7 |
| Women | 5207 | 53.3 |
| Age range, y | N | % |
| 0-9 | 1082 | 11.1 |
| 10-19 | 1583 | 16.2 |
| 20-29 | 1530 | 15.7 |
| 30-39 | 2663 | 27.3 |
| 40-49 | 1837 | 18.8 |
| 50-59 | 783 | 8.0 |
| 60-69 | 259 | 2.7 |
| ≥70 | 32 | 0.3 |

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

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

Example: Risk evaluation of Atypical Antipsychotics (AAP) for Hyperlipidemia

Other activities (1)
(Cooperation with other office)

Requests from other office
✓ Literature review
✓ Pharmacoepidemiological studies using electronic healthcare database
Targeted drug: Lithium Carbonate
- Drug for treatment of mania and mania status
- It can cause lithium poisoning if blood lithium level is uncontrolled

PMDA conducted a survey using claims data\(^1\).

The serum lithium level might have never been measured\(^2\) in 1,200 of 2,309 patients (52%) who were prescribed lithium carbonate

\(^1\) Data from January 2005 to December 2010 provided by Japan Medical Data Center Co., Ltd.
\(^2\) Lithium level measurement was defined as “performed” when the specific drug therapeutic management fee was recorded during the data period.

Guideline for conducting pharmacoepidemiological safety studies using electronic healthcare database

- Published in March 2014
- This guideline is intended to provide points to consider when PMDA and industries conduct pharmacoepidemiological studies for the assessment of safety issues


Sorry, Japanese only
Challenges in MIHARI Project

**Pilot Phase (2009-2013):**
- Developed framework for access to electronic healthcare database
- Assessed the feasibility of applying the well-known pharmacoepidemiological methods to drug safety assessment with Japanese electronic healthcare data

**Operational Phase (2014-2018):**
- To apply the framework into the current risk management process of drug safety
  - Strengthening cooperation with the office of review and the office of post-marketing safety in PMDA
- To establish an access to another database and additional pharmacoepidemiological methods using electronic healthcare data
  - Continuing to assess the feasibility of applying more advanced methods to drug safety assessment
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Overview of MID-NET Project

- MID-NET is a project initiated by MHLW / PMDA to establish the EMR DB network for post-marketing drug safety measures using electronic healthcare data.
Data categories in the MID-NET system

- **Database**
  - HIS data
  - Claims data
  - DPC data

**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

Standardization Anonymization

Common data model database for MID-NET

Hospitals

Original databases
- Medical record
- Labo test data
- Claims
- Others

Technical staff for MID-NET

⑤ Approve to send data

⑥ Send data

Central data center

⑦ View & Analysis

⑧ Output

individual level data

Summarized data

SAS® etc

SAS® etc

Summarized data

OR

individual level data

Summarized data
Personal data flow in MID-NET

Extraction of data w/ script

Central data center

Closed network

Hospital

- Hospital information system (HIS)
- Standardized data of HIS (HIS DB)
- DBMS

- Patient/outpatient Data (w/o ID)

Conversion to Statistical data

User

- Result of meta-analysis

Used only by Hospital

- w/ patient ID
- w/ name
- w/ address
- w/ zip code

Used by User

- w/o patient ID (sequential number added instead of ID)
- w/o name
- w/o address
- w/o zip code
- w/ date of all event (altered by random number)
- w/o correspondence table
The features of MID-NET

- **Strengths**
  - Available of various types of data (HIS data, Claims data and DPC data)
    - Including laboratory test results
  - Real time synchronization to medical record in the hospital

- **Limitations**
  - Number of hospitals participating in the MID-NET is currently limited (only 23 hospitals)
  - No link of data from different hospitals for a patient
Challenges for implementing MID-NET

Data standardization on medical information and quality check

Using localized Health Level Seven (HL-7) standard, but many ambiguous points

Clear rules for secondary use of EMRs with public understanding

PMDA will actively contribute to utilization of EMRs for public health promotion
Plans for full-scale utilization

<table>
<thead>
<tr>
<th>FY2011-2014</th>
<th>FY 2015</th>
<th>FY 2016</th>
<th>FY2017</th>
<th>FY2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Database developed</td>
<td>Data quality check</td>
<td>Verification of operation of the system and upgrade of the system</td>
<td>Trial utilization of MID-NET by PMDA / MHLW and 23 collaborating hospitals</td>
<td></td>
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</tbody>
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- Assessing the validity of health outcomes definitions
- Conducting pilot studies using MID-NET

Consideration of process for utilization of MID-NET by third parties such as academic researchers and industries

Full-scale utilization
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Point to consider in utilizing EMRs for drug evaluation -PMDA’s experiences in MIHARI-

- Data reliability
  - In addition to ensure an appropriateness of study design and data analysis, quality of database itself should be checked in advance.

- Selection of database
  - Characteristics of database (data holder, data periods, sample size, patients background, traceability, collected items, procedure for access etc.) should be confirmed in advance.
Proper planning and design of a study and analysis

✓ Refer to the guideline on conduct of pharmacoepidemiological study utilizing medical record database for drug safety assessment (published on March 31st, 2016)

• Make all efforts to understand how a target item was used in clinical practice
  ✓ Different diagnosis for claim
• Carefully consider clinical meaningfulness of an event definition
• Set a comparator for better interpretation of results
Selection of appropriate data period and timing for a study

✓ Generally, data for a few years
✓ A timing for a study
  • How many years after approval would be appropriate for a study purpose?

An integrated assessment based on results of more than one study

✓ Confirm in 2 or more studies
✓ Careful assessment with consideration of study limitations
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Future perspectives

• Accumulating more regulatory experiences on pharmacoepidemiological analysis
  – More PEpi study for a individual product
  – Implementation of MID-NET

• Promotion of PEpi analysis for safety assessment by industries
  – More guideline on Pepi
  – Scientific consultation on PEpi data

• Nurturing more pharmacoepidemiologist

• International cooperation for sharing experiences/ knowledge in utilizing those data for regulatory purposes
Active utilization of EHR databases toward advanced medical care

Regulatory decisions based on better scientific evidences
- Proper safety assessment utilizing EHR 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
Thank you for your attention

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