Challenges for Post-marketing Drug Safety Measures Using Electronic Healthcare Database in Japan

-MIHARI project and MID-NET project-

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Today’s Agenda

• Limitation of Current process of the post-marketing drug safety assessment
• MIHARI Project
• MID-NET Project
• Future Perspectives
Current process of drug safety measures in Japan

PMDA

Drug safety assessment using the conventional data sources

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

MHLW

Safety measure

Risk communication

MHLW: Ministry of Health, Labour and Welfare, Japan
Limitations of Current 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
MIHARI Project
Goal of MIHARI Project

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

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

PMDA

MHLW

Medical institutions

Safety measure

Risk communication
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

- 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
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 features 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
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
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 evaluation of Atypical Antipsychotics (AAP) for Hyperlipidemia

Other activities: Cooperation with other office

Requests from other office

- Literature review
- Pharmacoepidemiological studies using electronic healthcare database
PMDA alert based on survey using claims data

- 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.

Future direction of 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
Strengthening cooperation with other office

**Enhancement**
- Assignment to team in charge of epidemiology
- Requests from other offices have been increasing
MID-NET Project
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 from 23 hospitals

① PMDA sends programs to 23 hospitals
② Each hospital sends anonymized individual level data (w/o ID) and/or result of analysis to data center.

PMDA access and analyzes the data using exclusive PC
- Review results provided by hospitals
- Combine 23 results into 1
- Conduct additional analysis by using these results
Personal data flow in MID-NET

- **Hospital**: Hospital information system (HIS)
- **DBMS (HIS DB)**: Standardized data of HIS
- **Central data center**: Extraction of data w/ script
- **Conversion to Statistical data**: Patient/outpatient Data (w/o ID), Meta-analysis of A or B
- **Result of meta-analysis**: User

**Closed network**

- **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/o correspondence table, w/ date of all event (altered by random number)
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

Rules for secondary use of EMRs

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

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<tr>
<th>FY2011-2014</th>
<th>FY 2015</th>
<th>FY 2016</th>
<th>FY2017</th>
<th>FY2018</th>
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<tr>
<td>Database developed</td>
<td>Data quality check</td>
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<tr>
<td>Analysis system developed</td>
<td>Verification of operation of the system and upgrade of the system</td>
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<td>Trial utilization of MID-NET by PMDA / MHLW and 23 collaborating hospitals</td>
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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 |                          |                          |                          |                          |
Next steps

• 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

• Collaboration with other regulatory agencies
Utilization of e-data for better regulatory decision in:
- Development
- Pre-Approval
- Pharmacovigilance

"BIG DATA"-utilized Assessment & Regulation

- Accelerating Innovation
- Better Prediction
- Better B/R balance
- Minimizing costs
- More Successful Development
- Promoting Precision Medicine
Thank you for attention !