Drug Safety Assessment in the Era of ICT Advancement

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Priority area in PMDA

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)
Limitations of available data at the approval

- Too Few: small sample size
- Too Simple: strict dosage and administration
- Too brief: shorter period
- Too median-aged: age limitation
- Too Narrow: excluding special population

Rogers A.S., Drug Intel Clin Pharm., 1987

e.g.; Few elderly populations

Hypertension

Rofecoxib and Cardiovascular risk

Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial (APPROVe Trial)

Earlier detection of risk signal by analyzing electronic health records

Pharmacoepidemiological activities in all over the world

Europe

US

Observational Medical Outcomes Partnership

Sentinel Initiative

MID-NET®

Asian countries
MIHARI Project

To establish a framework of quantitative evaluation by pharmacoepidemiological methods using electronic healthcare data in PMDA

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

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

PMDA

MHLW

Medical institutions

Safety measure

Risk communication
Examples in MIAHRI project
Various database from different sources

Electronic medical records database
Dispensing claims database
Medical Institutions
Dispensing Pharmacy
Subscriber
Examination payment facility
Insurer
MHLW
National Claims Database

Healthcare Delivery
Copayment
Insurance fee
Issue Insurance cards
Payment Agency
Payment
Claims
Claims

Dispensing claims database
health insurance association’s claims database
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
Risk of Acute Asthma Attacks Associated With NSAIDs: A Self-Controlled Case Series.

Observation start:
- 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

Observation end:
- R0
- R1
- R2
- R3
- R4

Baseline Period:
- NSAIDs start date
- NSAIDs end date

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>
<tr>
<td>Age range, y</td>
<td></td>
<td></td>
</tr>
<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>≥70</td>
<td>259</td>
<td>2.7</td>
</tr>
<tr>
<td></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.

MIHARI Example 2: Cardiovascular risks associated with Dipeptidyl-Pepridase 4 inhibitors: a cohort study

Pharmacoepidemiology and Drug Safety; 24.SUPPL1.(529)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Exposure</th>
<th>No. of Cases</th>
<th>Adjusted HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myocardial infarction</td>
<td>BG</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>DPP–IV</td>
<td>75</td>
<td>1.11 (0.67, 1.82)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>BG</td>
<td>61</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>DPP–IV</td>
<td>171</td>
<td>1.03 (0.75, 1.42)</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>BG</td>
<td>23</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>DPP–IV</td>
<td>87</td>
<td>0.91(0.55, 1.52)</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>BG</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>DPP–IV</td>
<td>28</td>
<td>1.20(0.48, 2.99)</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>BG</td>
<td>0</td>
<td>Not available</td>
</tr>
<tr>
<td></td>
<td>DPP–IV</td>
<td>5</td>
<td>Not available</td>
</tr>
</tbody>
</table>
MIHARI Example 3: Risk evaluation of Atypical Antipsychotics (AAP) for Hyperlipidemia: A Sequence Symmetry Analysis

Adjusted sequence ratio (95 % CI)

MID-NET project
The Medical Information Database Network in Japan for a real-time assessment of drug safety (currently 4M patients)

An integrated real time EMR database with high quality

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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
Overview of MID-NET®

Onsite Center

1. Create program
2. Request for running program
3. Approve the request
4. Output
5. Approve to send data
6. Send data
7. View & Analysis
8. Output
9. Send only summarized data (not individual data)

Central data center

User

Hospitals

Technical staff for MID-NET

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

Standardization

Anonymization

Common data model database for MID-NET

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Data Quality of MID-NET

PMDA has worked with cooperative hospitals for assuring data quality of MID-NET

<table>
<thead>
<tr>
<th>Before quality management</th>
<th>After quality management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease order data</td>
<td>99.1%</td>
</tr>
<tr>
<td>Prescription order data</td>
<td>67.0%</td>
</tr>
<tr>
<td>Laboratory test data</td>
<td>55.8%</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease order data</td>
<td>99.9%</td>
</tr>
<tr>
<td>Prescription order data</td>
<td>100%</td>
</tr>
<tr>
<td>Laboratory test data</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
MID-NET® pilot: Ranmark® (Denosumab) Hypocalcemia

Launched (2012.4.17)

Spontaneous ADR reports
- Serious Hypocalcemia: 32 cases
- Death: 2 cases (~2012.8.31)

Traditional process

Dear healthcare professionals letter (2012.9.12)

If we utilize MID-NET…

- Quantitative risk assessment compared with control

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Number of patient with Hypocalcemia</th>
<th>Incidence proportion</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denosumab</td>
<td>190</td>
<td>93</td>
<td>0.489</td>
<td>1.35</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>245</td>
<td>89</td>
<td>0.363</td>
<td></td>
</tr>
</tbody>
</table>

Data from 3 hospitals (2013/7~12)
MID-NET pilot: Prazaxa® (dabigatran) GI-Bleeding

Compare risk of GI bleeding between Prazaxa and Warfarin

<table>
<thead>
<tr>
<th></th>
<th>Number of Prescription</th>
<th>Number of Patients</th>
<th>GI Bleeding</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patient</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Prazaxa</td>
<td>779</td>
<td>164</td>
<td>3</td>
<td>1.8%</td>
<td></td>
</tr>
<tr>
<td>warfarin</td>
<td>14,534</td>
<td>1,204</td>
<td>28</td>
<td>2.3%</td>
<td></td>
</tr>
</tbody>
</table>

Patients distribution based on Cr at the time of first prescription

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Normal -0.9mg/dL</th>
<th>Mild 0.9-1.35mg/dL</th>
<th>Moderate 1.35-2.7mg/dL</th>
<th>Severe 2.7-mg/dL</th>
<th>No Lab-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>prazaxa</td>
<td>164</td>
<td>57</td>
<td>34.8%</td>
<td>41</td>
<td>25.0%</td>
<td>7</td>
</tr>
<tr>
<td>warfarin</td>
<td>1,204</td>
<td>373</td>
<td>31.0%</td>
<td>304</td>
<td>25.2%</td>
<td>148</td>
</tr>
</tbody>
</table>
Comparison of SUV with Daklinza®

<table>
<thead>
<tr>
<th></th>
<th>Prescriptions</th>
<th>Patients</th>
<th>HCV-RNA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patient with Clinical examination</td>
</tr>
<tr>
<td>Harvoni</td>
<td>813</td>
<td>249</td>
<td>220</td>
</tr>
<tr>
<td>Daklinza</td>
<td>830</td>
<td>74</td>
<td>70</td>
</tr>
</tbody>
</table>

a) Percent to Patient  
b) SUV: Sustained virological response  
c) Percent to Patient with clinical examination

Comparison of renal dysfunction severity with Daklinza®

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>-0.9 mg/dL (Normal)</th>
<th>0.9-1.35 mg/dL</th>
<th>1.35-2.7 mg/dL</th>
<th>2.7-mg/dL</th>
<th>No labo test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Harvoni</td>
<td>249</td>
<td>170</td>
<td>68.3%</td>
<td>19</td>
<td>7.6%</td>
<td>1</td>
</tr>
<tr>
<td>Daklinza</td>
<td>74</td>
<td>39</td>
<td>52.7%</td>
<td>14</td>
<td>18.9%</td>
<td>0</td>
</tr>
</tbody>
</table>
Points to consider in utilizing EMRs for drug evaluation
-PMDA’s experiences in MIHARI-
Database 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
Patients Registries
Patients registries and Challenges

• Current 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 registries 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 | AMED

PMDA CIN-Working Group
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, for accelerating drug development, and for extending healthy life expectancy
Recent PMDA initiative
Big Data-utilized Assessment and Regulation
CDISC data submission on NDA formally started on October 1st, 2016

- **Establish disease models**
- **Identifying common risk factors among different drugs etc.**

**Modeling & Simulation:**
- Concentration-Response Model, PBPK: Physiologically-based Pharmacokinetic Model etc.

**CDISC data**

- **Database of Clinical Trial Results**
- **Analysis**

**NDA Review**
- More effective & High quality review
- B/R evaluation with raw data analysis

**Scientific Consultation**
- More efficient & Successful development
- Scientific advices based on the information obtained from analyses including M&S

**Cross-Products Analysis**
- More evidences & Advancing Regulatory Science
- Establish disease models
- Identifying common risk factors among different drugs etc.
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
More Successful Development

Archives of e-data
- EMR Data
- CDISC Data
Future Model
New technology for assessment

Examples

- Wearable devices
  - Smart watch etc.

- AI (artificial intelligence)
  - Watson etc.

More electronic data will be available and be accumulated!!
Organization for managing anonymized medical information on data utilization

- Hospital A
- Hospital B
- Hospital C

Private information

Organizations:
- PMDA
- Institutions
- Industries

Data Users:
- Review
- Safety Measures etc.
- Research etc.
- Drug development
- Pharmacovigillance etc.

Anonymized data for analysis

Utilization of real-world data for promoting public health


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Challenges

- Avoid being confounded by information
- Promoting standardization of data format for integrated assessments
- Establish standardized methods for utilization/analysis of the data/information

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

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

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

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

Better quality of Medical Care
- Maximize benefit/risk ratio
Regulatory Science Bridge


Stronger & More Complete Regulatory Science Bridge will help us in the future drug developments.
Ask