“Asian Ethnic Similarities and Differences: PMDA Point of View”

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China, Korea, Japan Tripartite Cooperation
Joint Statement of 3 Ministers Meeting (Apr. 2007)

- Clinical Researches

  Recognizing that East Asia has been rapidly gaining importance as a venue of today’s worldwide drug development, three Ministers affirmed the significance of cooperation among three countries on clinical researches, including clinical trials, especially in clarifying the ethnic factors on the clinical data, in order to facilitate drug development.
Current Projects -Working Group-

- Research on ethnic factors (Project coordinated by Japan)
  - Evaluate ethnic factors in drug clinical trial data to examine the possibility of sharing drug clinical trial data from three countries

- Information sharing (Project coordinated by Korea)
  - Mutual understanding of the regulatory frameworks for clinical trials in the three countries.

- Guideline on regional clinical trials (Project proposed by China)
  - Make guidelines on regional clinical trials with close cooperation with Korea and Japan.
Research on ethnic factors

PK comparison among East Asian and Caucasian populations
In the study, a part of ethnic variability was explained by the frequency differences in functional genetic polymorphisms of the drug metabolizing enzymes and transporters.

However, involvement of other factors in PK differences among populations has been suggested in some drugs, such as Moxifloxacin, Simvastatin, and Meloxicam.
To examine factors involved in PK differences of 3 drugs (Moxifloxacin, Simvastatin, and Meloxicam) among populations, prospective global PK studies under same protocol with strictly adjusted trial conditions were conducted in 4 countries (Japan, China, Korea, USA)

Japan:
- Toho University
- Kitasato University Research Center for Clinical Pharmacology
- National Institute of Health Science

China:
Peking University First Hospital

Korea
Seoul National University Hospital

USA:
SNBL Clinical Pharmacology Center
Example: Comparison of AUC_{inf} of Moxifloxacin

**Literature-based comparison (Tohkin Study group)**

Compared with Japanese
- Chinese: -0.6
- Chinese: -0.4
- Chinese: -0.2
- Chinese: 0
- Chinese: 0.2
- Chinese: 0.4

**Prospective PK Study (Kawai Study Group)**

Compared with Japanese
- Chinese: -0.2
- Korean: 0
- Caucasian: 0.2

90%CI

**Legend:**
- Chinese
- Korean
- Caucasian
Suggestions from the study results

- In order to assess ethnic differences in PK, a single protocol that controls extrinsic factors should be employed and uniformly applied to the study populations.

- Because polymorphisms of the relevant genes affect PK of a drug, it is recommended to know genotypes of study subjects and take them into consideration before evaluating the clinical data.
Japanese experiences to review data from Global Clinical Trials
Guidance: Basic Principles on Global Clinical Trials (GCTs) (September 28, 2007)

- Encourage Japan’s participation to GCTs from an early stage of drug developments
- Clear points to be considered in GCTs
- Promote conducting global clinical trials more appropriately in consideration of ethnic factors

Trends of GCTs including Japan

Numbers of All CTN


% of MRCTs

(DIA 2012 Collaborate to Innovate)
GCTs or Bridging-based Drug Approval

Number of Approved Drugs

Year


% of GCT
% of Bridging

Total
Bridging
GCT

DIA 2012
Collaborate to Innovate
## GCT-based Drug Approval (1)

<table>
<thead>
<tr>
<th>Name of Drug</th>
<th>Indication</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolterodine</td>
<td>Overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency</td>
<td>Apr. 2006</td>
</tr>
<tr>
<td>Losartan</td>
<td>Diabetic nephropathy with proteinuria and hypertension in patients with type 2 diabetes</td>
<td>Apr. 2006</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Adjuvant therapy for metastatic HER2-overexpressing breast cancer</td>
<td>Feb. 2008</td>
</tr>
<tr>
<td>Insulin glulisine</td>
<td>Diabetes mellitus</td>
<td>Apr. 2009</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>Pulmonary arterial hypertension</td>
<td>Oct. 2009</td>
</tr>
<tr>
<td>Peramivir *</td>
<td>Type A and Type B Influenza virus infection</td>
<td>Jan. 2010</td>
</tr>
<tr>
<td>Everolimus</td>
<td>Metastatic renal cell carcinoma</td>
<td>Jan. 2010</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>Metastatic colorectal carcinoma with wild-type KRAS tumors</td>
<td>Apr. 2010</td>
</tr>
<tr>
<td>Travoprost/Timolol*</td>
<td>Glaucoma</td>
<td>Apr. 2010</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>Advanced renal cell carcinoma</td>
<td>Jul. 2010</td>
</tr>
</tbody>
</table>

Red: Asian Global Clinical Trial  *: First Approval in the world
<table>
<thead>
<tr>
<th>Name of Drug</th>
<th>Indication</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laninamivir *</td>
<td>Type A and Type B Influenza virus infection</td>
<td>Sep. 2010</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>Newly diagnosed chronic myeloid leukemia in chronic phase</td>
<td>Nov. 2010</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Stroke and systemic embolism in patients with non-valvular atrial fibrillation</td>
<td>Jan. 2011</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Metastatic HER2-overexpressing gastric cancer</td>
<td>Mar. 2011</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>Parkinson's disease</td>
<td>Apr. 2011</td>
</tr>
<tr>
<td>Edoxaban*</td>
<td>Prevention of venous thromboembolism after major orthopedic surgery</td>
<td>Apr. 2011</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Chronic myeloid leukemia (CML)</td>
<td>Jun. 2011</td>
</tr>
<tr>
<td>Indacaterol</td>
<td>Chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.</td>
<td>Jul. 2011</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>Type 2 diabetes mellitus (adjunctive to diet and exercise)</td>
<td>Jul. 2011</td>
</tr>
</tbody>
</table>

Red: Asian Global Clinical Trial  *: First Approval in the world
### GCT-based Drug Approval (3)

<table>
<thead>
<tr>
<th>Name of Drug</th>
<th>Indication</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>EGFR-Positive unresectable or metastatic non-small cell lung cancer (NSCLC)</td>
<td>Nov. 2011</td>
</tr>
<tr>
<td>Everolimus</td>
<td>Progressive neuroendocrine tumors of pancreatic origin (PNET)</td>
<td>Dec. 2011</td>
</tr>
<tr>
<td>Denosumab</td>
<td>Bone complications in patients with multiple myeloma or solid tumour that has spread to the bone.</td>
<td>Jan. 2012</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Manic episodes associated with bipolar disorder</td>
<td>Jan. 2012</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Depression episodes associated with bipolar disorder</td>
<td>Feb. 2012</td>
</tr>
<tr>
<td>Exenatide</td>
<td>Type II diabetes mellitus (adjunctive to diet, exercise and treatment with SU)</td>
<td>Mar. 2012</td>
</tr>
</tbody>
</table>

Red: Asian Global Clinical Trial  
*: First Approval in the world

- Rapidly accumulating experiences of GCT data review
- Recognize an importance of East-Asian contribution
Example of East Asian GCT-based Drug Approval in Japan
Example 1:

Gefitinib for EGFR-Positive unresectable or metastatic non-small cell lung cancer (NSCLC)
**Gefitinib: IPASS study**

**PFS (Progression Free Survival: Overall population)**

<table>
<thead>
<tr>
<th>Enrolled population</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (randomized)</td>
<td>1217</td>
</tr>
<tr>
<td>Chinese</td>
<td>618</td>
</tr>
<tr>
<td>Japanese</td>
<td>233</td>
</tr>
<tr>
<td>Other Asian</td>
<td>363</td>
</tr>
<tr>
<td>Others</td>
<td>3</td>
</tr>
</tbody>
</table>

- Confirmed the non-inferiority of gefitinib to calboplastin+paclitaxel
# IPASS: PFS (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Gefitinib</th>
<th>Calboplatin+Paclitaxel</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>5.7 [5.4, 6.8] (n=609)</td>
<td>5.8 [5.6, 6.4] (n=608)</td>
<td>0.741 [0.651, 0.845]</td>
</tr>
<tr>
<td>Japanese</td>
<td>6.9 [4.4, 8.4] (n=114)</td>
<td>6.8 [5.6, 7.0] (n=119)</td>
<td>0.693 [0.510, 0.942]</td>
</tr>
</tbody>
</table>

**Overall population**

- Gefitinib
- Calboplatin+Paclitaxel

**Japanese population**

- Gefitinib
- Calboplatin+Paclitaxel

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DIA 2012
Collaborate to Innovate
IPASS: Efficacy (EGFR Mutation)

- Genetic samples were collected from 653 patients (56%)
- Samples from 437 patients (36%) were available for genetic data review

PFS: Overall population

### EGFR (+)
- Gefitinib
- Calboplatin + Paclitaxel

### EGFR (-)
- Calboplatin + Paclitaxel
- Gefitinib
IPASS: Efficacy (EGFR Mutation)

- EGFR mutation status was examined in only 91 Japanese patients (39% of total Japanese patients)

PFS: Japanese population

**EGFR (+)**

- Gefitinib
- Calboplastin+Paclitaxel

**EGFR (-)**

- Calboplastin+Paclitaxel
- Gefitinib
Other studies available for review

- Independent prospective studies (Investigator-initiative trial) support the efficacy of gefitinib in EGFR(+) Japanese patients

<table>
<thead>
<tr>
<th></th>
<th>Gefitinib (N = 114)</th>
<th>Carboplatin–Paclitaxel (N = 114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exon 19 deletion</td>
<td>58 (50.9)</td>
<td>59 (51.8)</td>
</tr>
<tr>
<td>L858R</td>
<td>49 (43.0)</td>
<td>48 (42.1)</td>
</tr>
<tr>
<td>Others</td>
<td>7 (6.1)</td>
<td>7 (6.1)</td>
</tr>
</tbody>
</table>
Summary

- Efficacy of gefitinib was confirmed in IPASS study (mainly including East-Asian patients)
- No major difference was shown between Japanese and overall population
- Favorable response were shown in EGFR(+) patients
- Independent prospective studies support efficacy of gefitinib in EGFR(+) - Japanese patients

The indication of gefitinib was revised to limit to the EGFR(+) patients
Example 2:

Edoxaban for the prevention of venous thromboembolism (VTE) in patients with total knee arthroplasty, total hip arthroplasty and hip fracture surgery
Clinical Data Package

- **Japan**
  - Phase I
  - CP Study
  - TKR Phase IIb
  - THR Phase III
  - HFS Phase III

- **Chinese Taipei**
  - CP Study
  - GCT: Phase III
  - GCT: Phase IIb

- **Hong Kong**
  - Phase I

- **Foreign**
  - Phase I
  - CP Study
  - Phase IIa

- Most of the enrolled patients were Japanese.
- Similar responses (efficacy/safety) were observed between Japan and Chinese Taipei.
GCTs contributes to resolve Drug Lag

Approved in FY2009-FY2011 (as of Sep. 30th)

* Difference of NDA application date between USA and Japan is calculated. The difference is assumed 0, if a drug is not approved in USA.
New Guidance
“Basic Principles on Global Clinical Trials (Reference Cases) (Draft)”

- MHLW/PMDA is preparing to publish another new guidance document
- Contents of the document is based on recently accumulated scientific data and our experiences
- The document is intended to further promote an understanding of the 2007 notification and ensure Japan’s smooth participation in global drug development activities at an early stage as well as smooth and proper implementation of East-Asian global clinical trials
Examples of Expected Discussion Points (1)

- Points to consider in conducting East-Asian global clinical trials
- Recommended therapeutic area for East-Asian global clinical trials
- How to develop global drug development strategies based on data of interethnic comparison of pharmacokinetics
- Points to consider in comparing PK data between different ethnicities
- Points to consider in evaluating the results of a global clinical trial
Examples of Expected Discussion Points (2)

- Points to consider in conducting a global clinical trial when PK exposure is different between Japanese and non-Japanese subjects
- Points consider in evaluating the data of Japanese subjects living overseas enrolled in overseas studies
- Points to consider when the target sample size of Japanese is not achieved in a global clinical trial
- Points to consider in participating in a large-scale global clinical trial using a true endpoint such as survival time
- Points to consider in the required Japanese sample size to evaluate long-term safety of a drug that clinical trials are mainly conducted as a global clinical trial
Conclusion

- For a better assessment regarding effects of ethnic factors on drug efficacy and safety, more scientific data should be accumulated.

- A GCT under the same protocol will provide valuable information to examine ethnic similarities/differences for regulatory review.
Acknowledgement

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Thank you for your attention