Morakot Papassiripan, MSc, Thailand

- Reviewer, Biological Products Sub-Division, Bureau of Drug Control of Food and Drug Administration (Thai FDA), Ministry of Public Health Thailand
Clinical experience with EPO products approved via the generics pathway: the experience in Thailand

Morakot Papassiripan, PhD
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Introduction (1)

• In 1988, Erythropoiesis Stimulating Agent (ESA) was introduced and became the standard treatment for anemia in patients with Chronic Kidney Disease (CKD)

• In mid-1990s, a shift from the IV to the SC route of ESA occurred in many countries due to clinical and economic reasons

• In 2002, the Thai Health Product Vigillane Center received the 1st case of Pure Red Cell Aplasia (PRCA)

• In 1998, the original ESA product formulation using PS-80 as a stabilizer in stead of HAS
Introduction (2)

- In 1998–2003, the cases of EPO antibody-mediated PRCA were increased in CKD patients receiving one specific Eprex formulation [uncoated Polysorbate -80 (PS-80) PFS] by the SC route
- In March 2004, uncoated PS-80 PFS Eprex formulation was completely removed from the market
- The worldwide incidence rate of EPO Ab-mediated PRCA reports were decreased, except in Thailand
- October 2008, 85 patients were reported in lack of efficacy in relation to ESAs in Thailand
What are the issues in Thailand

• 15 brands of EPO Alfa and 1 brand of EPO Beta were registered in Thailand

• Poor people can receive EPO products because the cost is lower than the original product

• But, what problem does Thai FDA find?
“Biosimilar recombinant human erythropoietin induces the production of neutralizing antibodies”

• “Studied 30 patients with CKD treated by subcutaneous injection with biosimilar r-Hu-EPO and who developed a sudden loss of efficacy ...”

• “Sera from 23 of these patients were positive for r-Hu-EPO neutralizing antibodies, and their bone marrow biopsies, indicated PRCA ...”
“Biosimilar recombinant human erythropoietin induces the production of neutralizing antibodies”

• “Thus, subcutaneous injection of biosimilar r-Hu-EPO can cause largely adverse immunological effects a large ...”

• “Long-term pharmacovigilance study is necessary to monitor and ensure patient safety for these agents”

• “Estimation risk for anti-r-Hu-EPO associated PRCA was 23/59,990”
“Biosimilar recombinant human erythropoietin induces the production of neutralizing antibodies”

• “An estimation of the actual cases using biosimilar r-Hu-EPO denominator with this complication was 1:2,608”

• “The results could not provide sufficient information to determine exactly which specific biosimilar products are directly responsible for causing anti-r-Hu-EPO associated PRCA...

• “However, we can clearly state that repeated subcutaneous injection of biosimilar agents could result in the development of anti-r-Hu-EPO associated PRCA”
What are the solutions? (1)

• There are 16 EPO brands but none are biosimilar (even though Binocrit which was registered by the same pathway as the other EPO products) because of ...
Development of registration pathway

- **Chemical drug pathway (Generic)**
  - Q, NC, C x1

- **New Drug pathway**
  - Q, NC, C x2

- **ACTD/ACTR**
  - Full application
  - Q, NC, C x2

- **Biosimilar guideline**

- **< 1995**
  - EPO original registered in 1990

- **1995**

- **2009**
  - … Follow-on EPO registered …

- **2013**
  - MAB
What are the solutions? (2)

• Legal actions
  – Revised regulations
    • 2009 ASEAN Harmonization/ICH
    • 2013 Biosimilar registration pathway
      – New products of EPO will submit in the stand alone pathway (new biological product pathway) / the biosimilar pathway
      – Re-assessment process for the EPO products in the market
      – Pharmacovigillance system
  • Non-legal actions
    – Dear doctor letter, Alert letter
Pharmacovigilance

Report
(mail, email, FAX,)
Online report, report form

- Since 1983
  - Spontaneous passive surveillance
    - Safety drug monitoring program
  - Active surveillance
    - Intensive drug monitoring
    - Registry

Sources of reports
(hospital, drugstore)
Marketing Authorization Holder

Dear doctor letter
Annual report
Bulletin

Thai FDA : HPVC
Current situation (1)

<table>
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<tr>
<th>Year</th>
<th>Number of PRCA case</th>
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**Current situation (2)**

PRCA cases (301) (2001–2015)

Confirmed cases *AB positive (201)

Suspected cases (100)

PRCA/LOE

*Thai registry incidence = 1.7 : 1,000
Factors influencing immunogenicity

Product-related factors
- Protein (structure, primary sequence, novel epitopes, glycosylation, oxidation, deamidation)
- Product impurities, formulation, aggregation, degradation
- Protein properties, e.g. immunostimulatory, replacement therapy, physiologically important
- Administration: (dose, route (subcutaneous for EPO), frequency of administration and duration of therapy
- Interchangeability

Patient-related factors
- Age
- Gender
- Genetic phenotype
- Ethnic sensitivity (IFN-alpha 2a more immunogenic in Chinese compared to Caucasian hepatitis patients 39% vs 14%)
- Immune status
- Disease
What are the possible causes for the high reporting rate of these events in Thailand?

- Product?
- Quality?
- Formulation?
- Storage and handling?
- Route of administration?
- Interchangeability of the products?
- Genetic phenotype?
Summary

**Product**
- How could Thai FDA solve this problem?
  - (Re-evaluation process, Biosimilar pathway)

**Clinical practice**
- Interchangeability
- Subcutaneous use
  - (Cooperate with the clinicians)

**Consider**
- Government’s health budget supported
  - (If the price of product is over difference, the biosimilar product is necessary for use)
- Patient-related factors (in case of subcutaneous used)
  - Far and hard to go the hospital and receive drug
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THANK YOU
FOR YOUR ATTENTION