Challenges in Conducting a Multinational European Study of Severe Hypersensitivity Reactions Among Recipients of Intravenous Iron


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CONFLICTS OF INTEREST

• The PHARMO Institute of Drug Outcomes Research is an independent nonprofit research organization that does not work for government agencies and pharmaceutical companies.
• The Center for Pharmacoepidemiology, Karolinska Institute grants fellowships to pharmaceutical companies, regulatory authorities, and contract research organizations for performance of drug safety and drug utilization studies. AT is a staff member of Cefor des Gouvèze, University of Orléans. She has conducted research funded by pharmaceutical companies.
• Anthes University receives institutional funding for research projects from several public and private entities.
• GoH, M., and P. work as employees in the Department of Internal Medicine—Grp. University, Cologne. Faculty of Medicine and University hospital Cologne, Germany.
• The Leiden Institute for Prevention Research and Epidemiology—BEPS occasionally conducts studies financed by the pharmaceutical industry, mostly R&D requested by health authorities.
• AC is an employee of the Information System for Health Care Data (DaTraV), which processes applications from RTI-HS and changes user fees.
• MF is an employee of Penfluvine, a service provider specializing in pharmacovigilance services and consulting. Penfluvine received a donation from a consortium of manufacturers of intravenous iron compounds for the coordination of the scientific committee.

BACKGROUND

• Severe hypersensitivity reactions (SHRs) in intravenous (IV) iron treatments are rare and are poorly characterized. Safety concern in Europe. A multidisciplinary study approach is required to evaluate this rare condition. The registry-based multinational pharmacovigilance safety study (PASS) with multiple sponsors will assess the risk of SHRs in IV iron users in Europe (EURIS 20720). Results will be available in 2022.

OBJECTIVES

• To describe the cohort attrition of IV iron users and challenges encountered in setting up the PASS.

METHODS

Study Setting

Table 1. IV Iron Treatment and Severe Hypersensitivity Reactions (Preliminary)

<table>
<thead>
<tr>
<th>W Iron Treatment</th>
<th>Demark’s National Registers</th>
<th>DAnE Database, France</th>
<th>PHARMO, Netherlands</th>
<th>Swedish National Registers</th>
<th>GoED, Germany</th>
<th>KHN, Germany</th>
<th>DAnE/DaTraV, Germany</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>9,808</td>
<td>7,596</td>
<td>5,876</td>
<td>42,466</td>
<td>146,826</td>
<td>33,419</td>
<td>352,450</td>
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</tr>
<tr>
<td>Events (n=yr)</td>
<td>5 &lt; 5 0 5 &lt; 5 5 0</td>
<td>6 0 &lt; 5 0 5 0</td>
<td>6 0 &lt; 5 0 5 0</td>
<td>5 0 &lt; 5 0 5 0</td>
<td>3 0 &lt; 5 0 5 0</td>
<td>14 104</td>
<td>16 104</td>
<td></td>
</tr>
<tr>
<td>Patients (n=yr)</td>
<td>2,169</td>
<td>22,826</td>
<td>1,853</td>
<td>20,822</td>
<td>67,856</td>
<td>32,756</td>
<td>148,104</td>
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<tr>
<td>Events (n=yr)</td>
<td>&lt; 5 0 &lt; 5 0 &lt; 5 0</td>
<td>&lt; 5 0 &lt; 5 0 &lt; 5 0</td>
<td>&lt; 5 0 &lt; 5 0 &lt; 5 0</td>
<td>&lt; 5 0 &lt; 5 0 &lt; 5 0</td>
<td>&lt; 5 0 &lt; 5 0 &lt; 5 0</td>
<td>3 0 &lt; 5 0 &lt; 5 0</td>
<td>3 &lt; 5 0 &lt; 5 0</td>
<td></td>
</tr>
<tr>
<td>First or second n=yr</td>
<td>4,125</td>
<td>2,017</td>
<td>3,120</td>
<td>3,120</td>
<td>6,771</td>
<td>3,120</td>
<td>2,017</td>
<td>3 &lt; 5 0 &lt; 5 0</td>
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<tr>
<td>Events (n=yr)</td>
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<td>0 &lt; 5 0 &lt; 5 0 &lt; 5 0</td>
<td>0 &lt; 5 0 &lt; 5 0 &lt; 5 0</td>
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<td>0 &lt; 5 0 &lt; 5 0 &lt; 5 0</td>
<td>0 &lt; 5 0 &lt; 5 0 &lt; 5 0</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 1. IV Iron Treatment and Severe Hypersensitivity Reactions (Preliminary)**

**W Iron Treatments** includes all IV iron treatments active in the database.

**Demar’s National Registers** includes the Danish National Registry for patients aged 18 years or older.

**DAnE Database, France** includes the French national pharmacovigilance database.

**PHARMO, Netherlands** includes the Dutch national pharmacovigilance database.

**Swedish National Registers** includes the Swedish national pharmacovigilance database.

**GoED, Germany** includes the German national pharmacovigilance database.

**KHN, Germany** includes the German national pharmacovigilance database.

**DAnE/DaTraV, Germany** includes the Danish National Medicines Agency database.

**Overall** includes all patients and events across all databases.

<table>
<thead>
<tr>
<th>CRITERION A</th>
<th>CRITERION B</th>
<th>CRITERION C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aged 18 years or older at cohort entry date</td>
<td>Aged 18 years or older at cohort entry date</td>
<td>Aged 18 years or older at cohort entry date</td>
</tr>
</tbody>
</table>

**CONCLUSIONS**

• The risk of SHRs due to penicillin administration has been described in the literature. A cohort of IV penicillin users was used, where feasible, to assess the performance of the SHR identification algorithm.
• The algorithms used to identify SHRs rely on both diagnostic codes and SHR criteria (e.g., symptoms, signs, and treatments).
• Harmonization and local adaptation of outcomes and variable definitions across all research centers was performed.
• Distributed analyses were conducted in each database using a common protocol and analysis plan with local adaptations.

REFERENCES


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