Pulmonary hypertension, rare diseases and EU policies

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DISCLOSURES

• Speaker, consultant, or steering committee member:
  – Acceleron, AOP, Bayer, Daiichi Sankyo, Ferrer, Inari, Janssen, MSD, Pfizer

• Research grants:
  – Janssen
PULMONARY HYPERTENSION, RARE DISEASES
AND EU POLICIES

• What is PH? When to suspect PH?
• From a frequent anomaly to rare forms of PH
  – Pulmonary arterial hypertension (PAH)
• Remarkable orphan drug development - Still high mortality
  – Vasodilators
  – Pipeline
• Knowledge dissemination
  – Practice guidelines and statements
  – 1st-6th World Symposia on PH
• National policies vs. EU policies
• Key messages and action points
WHAT IS PULMONARY HYPERTENSION (PH)?
WHEN TO SUSPECT PH?

- Right Sided Heart Failure
  - Fatigue
  - Elevated Venous Pressure
  - Ascites
  - Enlarged Liver & Spleen
  - Distended Jugular Veins
  - Anorexia & Complaints of GI Distress
  - Swelling in Hands & Fingers
  - Dependent Edema
PH IS A FREQUENT ANOMALY (1%)

BUT SOME FORMS ARE RARE (<1/2,000)

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Pulmonary arterial hypertension (PAH)</td>
<td>50 per million</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1/20,000</td>
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<tr>
<td>Group 2</td>
<td>Pulmonary hypertension due to left heart disease</td>
<td>very frequent</td>
</tr>
<tr>
<td>Group 3</td>
<td>Pulmonary hypertension due to lung disease</td>
<td>frequent</td>
</tr>
<tr>
<td>Group 4</td>
<td>Chronic thromboembolic pulmonary hypertension (CTEPH)</td>
<td>30 per million</td>
</tr>
<tr>
<td>Group 5</td>
<td>PH due to unclear or multifactorial causes</td>
<td>very rare</td>
</tr>
</tbody>
</table>

_Galie et al, EHJ and ERJ 2015_
PAH TREATMENTS (vasodilators)

DESPITE DRUG DISCOVERY AND EDUCATION PAH REMAINS A DEVASTATING CONDITION

Survival rates

<table>
<thead>
<tr>
<th>Survival rates</th>
<th>1 year</th>
<th>2 years</th>
<th>3 years</th>
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<tr>
<td></td>
<td>82.9%</td>
<td>67.1%</td>
<td>58.2%</td>
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<tr>
<td>(95% CI)</td>
<td>(72.4 – 95.0)</td>
<td>(57.1 – 78.8)</td>
<td>(49.0 – 69.3)</td>
</tr>
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</table>

10% mortality per year

OTHER APPROACHES (targeting proliferation)

- PDGF, VEGF, EGF
  - Tyrosine kinase inhibitors
    - Imatinib

- BMPR-II / TGF-β axis
  - Familial PAH (BMPR2 mutation)
  - IPAH: ↓ expression BMPR2 signal
    - BMPR2 signaling
    - Sotatercept [TGFβ/activin ligand trap]

- Inflammation
  - Cytokines, Chemokines
  - Lymphocytes neogenesis
    - Tolicizumab
    - Ubenimex
    - Nrf2 activator and NFκB inh
    - Leukotriene B4

- Oxidative stress
  - Resistance to apoptosis
    - Bardoxolone, ASK-1 inhibitor
    - Nrf2 activator and NFκB inh
    - Selonsertib

- Mitochondrial metabolism

- Vasoactive mediators
  - Serotonin (5-HT), Thromboxane A2
  - Vaso-intestinal peptide, Apelin
    - SSRI, 5-HT receptors antagonists

- OTHER APPROACHES (targeting proliferation)
  - Tacrolimus
  - Apoptosis signal-regulating kinase-1
  - Rituximab

PAH/PH/CTEPH GUIDELINES - STATEMENTS

2004
ESC Guidelines
Guidelines on diagnosis and treatment of pulmonary arterial hypertension
The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology

2009
ESC/ERS GUIDELINES
Guidelines for the diagnosis and treatment of pulmonary hypertension
The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT)

2015
ESC/ERS GUIDELINES
2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)
Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT)

2017
ERS OFFICIAL DOCUMENT
ERS STATEMENT
CrossMark
2017 An official European Respiratory Society statement: pulmonary haemodynamics during exercise

2019
ERS statement on exercise training and rehabilitation in patients with severe chronic pulmonary hypertension

2021
ERS statement on chronic thromboembolic pulmonary hypertension

ANNOUNCED
2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
RARE DISEASE POLICIES IN EU

Fig. 1. Evolution of rare disease policy in Europe (December 2014) [4].

Rodwell & Aymé, Biochimica et Biophysica Acta 2015
FR as the best example of a large country with a well-defined RD plan

https://respifil.fr
UK: another large country with advanced care organisation
ERLUNG is made up of 9 Core Networks representing the diversity of diseases and conditions affecting the lungs, and 9 Functional Committees that coordinate transversal activities affecting all of the current and future Core Networks.

- **CF**: Cystic Fibrosis
- **PCD**: Primary Ciliary Dyskinesia
- **nCF-BE**: Non-CF Bronchiectasis
- **PH**: Pulmonary Hypertension
- **ILD**: Interstitial Lung Disease
- **CLAD**: Chronic Lung Allograft Dysfunction
- **MSTO**: Mesothelioma
- **AATD**: Alpha-1 AntiTrypsin Deficiency
- **ORLD**: Other Rare Lung Diseases

1. Research & Clinical Trials
2. Clinical Guidelines & Best Practice of Care
3. Registries & Biobanks
4. Communication & Outreach
5. Ethical Issues
6. Cross Border Care
7. Professional Training & Continued Medical Education
8. Patient Recorded Outcomes (PROs) & Quality of Life
9. Quality Management
Domain: PH

- 27 full members
- 4 affiliated partners
- 4 UK supporting partners

Severe Pulmonary Hypertension Management Across Europe (PHAROS): an ERS Clinical Research Collaboration

Olivier Sitbon, Abilio Reis, Marc Humbert, Anton Vonk Noordegraaf, and Marion Delcroix, on behalf of the PHAROS Clinical Research Collaboration

Sitbon et al, Eur Respir J 2020
Key messages

- **rare** The prevalence of PAH averages 50 per million inhabitants
- **drugs** 14 agents approved in the last 25 years
- **fatal** Median survival still averages 6 years
- **EU** Diverse care organisations and recognition/ignorance of expertise
ACTION POINTS

• **Stronger EU incentives for — and control of — the implementation of national RD plans, including**
  – Clear identification and financing of dedicated expert centres
  – Improved RD care organisation and audits

• **Expedited new drugs approval/reimbursement**
  – Closer collaboration between EMA and EU Member States

• **More effective incentives on RD research**
  – Not restricted to genetic diseases; embedded in the EU scientific societies

• **ERNs**
  – Less administrative burden, more transparency, more coordinated actions between ERNs
  – Global solutions concerning registries, data sharing regulation, …
  – Reconsidering the funding structure (project-driven, …)