What’s on the horizon: Clinical trials and new treatments
St. Paul, Minn. 2017 PHA on the Road

Session Description:
The treatment options for PH continue to expand as a result of doctors and scientists apply new knowledge about who gets PH and how the disease “starts” in different types of patients to clinical trials of new drugs. This session will review current PH classification and drugs. The session will also cover clinical trials in PH — how to find out what trials exists and where. New trends in PH therapy will be described.

Learning Objectives:
• A clinical trial - what, where and why?
• Brief update of PH classification
• Overview: current clinical trials and treatment trends
• Lightning Round: Q/A will allow all to get their questions answered. Please participate!

What exactly is a clinical trial?
• The World Health Organization (WHO) definition for a clinical trial is... “Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.”

Where do I find out about clinical trials?
• PHA Website – www.PHASociation.org/ClinicalTrials
• www.ClinicalTrials.Gov
• Mayo Pulmonary Hypertension website

The benefits of participating in a clinical trial?
• Generate knowledge that will help us understand, diagnose and/or treat PH now and in the future
• Without clinical research we are unable to improve our understanding of human disease
• Early access to new tests or treatments
• Frequent contact with healthcare providers

The risks of participating in a clinical trial?
• Early access to new tests or treatments
  • Side effects from medications or adverse effects from study procedures
• Frequent contact with health care providers
  • Time investment
• The test or treatment may be ineffective or even harmful

Pulmonary hypertension classification (Groups)
1. Pulmonary arterial hypertension (PAH)
   a. Idiopathic PAH (IPAH)
   b. Heritable PAH (HPAH)
   c. PAH associated with connective tissue diseases, liver disease, HIV infection, congenital heart diseases, and exposure to certain drugs/toxins
   d. Pulmonary veno-occlusive (PVOD) and pulmonary capillary hemagiomatosis (PCH)
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2. PH due to left heart disease (heart failure/valve disease)
3. PH due to chronic lung disease (emphysema or interstitial lung diseases)
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Unclear mechanisms (hematology problems/sarcoidosis/ splenectomy/renal disease)

### Treatment Options

*A number of background therapies are available before starting PH-specific drugs and may help manage PH symptoms:*

- Oxygen is prescribed to patients who have evidence of low blood oxygen levels (i.e. low oxygen saturation).
  Some patients use oxygen all the time while others may only need oxygen with exertion and/or during sleep.
- Digoxin may be prescribed to help with right heart failure.
- Warfarin (or Coumadin®) is sometimes prescribed for patients with certain types of PAH (e.g. IPAH or hereditary PAH) to prevent blood clots in the lungs. Patients who have a history of blood clots may also be prescribed warfarin.
- Diuretics such as furosemide and spironolactone are used to prevent fluid retention.

**Pulmonary Artery Hypertension-specific therapies (Mainly Group I).**

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
<th>Route</th>
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<tbody>
<tr>
<td>1995</td>
<td>Epoprostenol</td>
<td>Intravenous</td>
</tr>
<tr>
<td>2000</td>
<td>Iloprost</td>
<td>Inhaled</td>
</tr>
<tr>
<td>2001</td>
<td>Treprostinil</td>
<td>Oral</td>
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<tr>
<td>2002</td>
<td>Treprostinil</td>
<td>Subcutaneous</td>
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<tr>
<td>2004</td>
<td>Sildenafil</td>
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<td>2005</td>
<td>Tadalafil</td>
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<tr>
<td>2007</td>
<td>Ambrisentan</td>
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<td>2009</td>
<td>Macitentan</td>
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<td>2010</td>
<td>Riociguat</td>
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<td>2013</td>
<td>Selexipag</td>
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<td>2014</td>
<td>Treprostinil</td>
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<tr>
<td>2015</td>
<td>Treprostinil</td>
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</tbody>
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- Calcium channel blockers
  - ONLY for those patients who have documented response to vasodilators during right heart catheterization.
- Synthetic prostacyclins, prostacyclin analogues, and prostacyclin receptor agonists
  - Epoprostenol (Flolan® and Veletri®) – Intravenous
  - Iloprost (Ventavis®) – Inhaled, 6 to 9 times a day
  - Selexipag (Uptravi®) – Oral, twice daily
  - Treprostinil (Remodulin®) – Intravenous or subcutaneous
  - Treprostinil (Tyvaso®) – Inhaled, 4 times a day
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○ Treprostinil (Orenitram®) – Oral, 2-3 times a day

● Endothelin Receptor Antagonists
  ○ Ambrisentan (Letairis®) – Oral, once daily
  ○ Bosentan (Tracleer®) – Oral, twice daily
  ○ Macitentan (Opsumit®) – Oral, once daily

● Phosphodiesterase-5 Inhibitors
  ○ Sildenafil (Revatio®) – Oral, three times a day
  ○ Tadalafil (Adcirca®) – Oral, two pills, once a day

● Soluble Guanylate Cyclase Stimulators
  ○ Riociguat (Adempas®) – oral, three times a day

Ongoing areas of clinical research and current trends in PH treatment

● Different combinations of drugs
● Transitions from one PH drug to another
● Diastolic dysfunction emphasis
● Balloon angioplasty
● Ongoing/Future research

Inflammation/Immunity/Mitochondrial dysfunction/ Blood deficiencies/ Neurohormonal axis:

More and more research is focused on the impact of immune cells and inflammation in the development and progression of PAH. Current evidence has revealed that:

● Patients with PAH have higher levels of inflammatory proteins in their blood and higher levels of immune cells in and around the small arteries of the lung
● Blood deficiencies related to PAH have been shown to impact PAH
● Sympathetic nerve endings and hormones can affect the pulmonary arteries. Current therapies that target hormonal and immune pathways that are under investigation include:
  1. Ubenimex (Bestatin®) - inhibits leukotriene B4
  2. Rituximab inhibits B-cells (especially in scleroderma)
  3. Tocilizumab (Actemra®) - monoclonal antibody to IL-6
  4. Bardoxolone methyl – LARIAT study for connective tissue disease–associated PAH
  5. Iron deficiency – correct the deficiency with infused or oral iron
  6. Pulmonary artery denervation (PADN) procedure – ablating sympathetic tone to the pulmonary arteries to vasodilate arteries

Additional Resources

● [www.PHAssociation.org/ClinicalTrials](http://www.PHAssociation.org/ClinicalTrials)
● [Clinicaltrials.gov](http://Clinicaltrials.gov)
● [Mayoclinic.org/pulmonary hypertension](http://Mayoclinic.org/pulmonary hypertension)
● PHA Classroom Recording: Drug Development, treatments on the Horizon and Stem Cells
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