Medical Management of CTEPH: What is its role?

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Disclosures

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Research Support: Aires, Gilead Sciences, Lung Biotechnology, United Therapeutics

Off-Label Discussion
Objective

• Define the role of medical management in patients with CTEPH
The sGC stimulator riociguat became the first medical therapy approved for CTEPH (WHO Group 4) includes which of the following indications?

A. High PVR bridged to surgery  
B. Exercise-induced PH with CTE disease  
C. High operative risk due to comorbidity  
D. Residual PH after PEA
CHEST study: objectives and design

**CHronic ThromboEmbolic Pulmonary Hypertension sGC-Stimulator Trial**

**Objectives**

- Evaluate the efficacy of riociguat in the treatment of patients with inoperable CTEPH or persistent/recurrent PH after PEA

**Design**

- Multicenter, double-blind, randomized, placebo-controlled study (CHEST-1)
  - 89 centers across 26 countries in Europe, South America, North America, Asia, and Australia

**Outcomes**

- **Primary outcome**: Change in 6MWD from baseline at Week 16
- **Secondary outcomes**: NT-proBNP, WHO FC, Borg dyspnea score, QoL assessments, time to clinical worsening, safety variables
  - Hemodynamic parameters (RHC): PVR, RAP, mPAP, cardiac index, MAP, PCWP

**Statistical analysis**

- **Primary endpoint**: ANCOVA followed by non-parametric stratified Wilcoxon test
- **Secondary endpoints**: Hierarchical testing procedure: PVR, NT-proBNP, WHO FC, time to clinical worsening, Borg dyspnea score, EQ-5D, and LPH questionnaires
  - NT-proBNP, EQ-5D, LPH, and hemodynamics analyzed using ANCOVA followed by non-parametric stratified Wilcoxon test
  - WHO FC and Borg dyspnea analyzed using stratified Wilcoxon test
  - Time to clinical worsening was analyzed using a stratified log-rank test

**Correlation analyses**

- Pearson correlation coefficient was used to assess the correlation between Δ6MWD and ΔPVR, and Δ6MWD and ΔCI

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## CHEST baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Inoperable CTEPH</th>
<th>Persistent/recurrent PH after PEA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Placebo</td>
<td>n</td>
</tr>
<tr>
<td>Age, years</td>
<td>88</td>
<td>59 (13)</td>
<td>173</td>
</tr>
<tr>
<td>Female (%)</td>
<td>88</td>
<td>61</td>
<td>173</td>
</tr>
<tr>
<td>6MWD, m</td>
<td>88</td>
<td>356 (75)</td>
<td>173</td>
</tr>
<tr>
<td>WHO FC I/II/III/IV (%)</td>
<td>87</td>
<td>0/28/68/2a</td>
<td>173</td>
</tr>
<tr>
<td>PVR, dyn·s·cm⁻⁵</td>
<td>82</td>
<td>779 (401)</td>
<td>151</td>
</tr>
</tbody>
</table>

aOne patient with missing data at baseline.
Data are mean (standard deviation), except for gender and WHO FC (%).

**Total Population**

+46 m  
p<0.0001  
(95% CI: 25–67 m)

(n=173/88)

**Inoperable CTEPH**

+54 m  
(95% CI: 29–78 m)

(n=52/20)

**Persistent/recurrent CTEPH after PEA**

+26 m  
(95% CI: −16–68 m)

(n=121/68)

Bars represent mean change from baseline (±SEM); LS mean treatment effect taken from ANCOVA.

Mean change from baseline in PVR ±SEM (dyn·s·cm⁻⁵)

Bars represent mean change from baseline (±SEM); LS mean treatment effect taken from ANCOVA.

-246 dyn·s·cm⁻⁵
p<0.0001
(95% CI: −303 to −190 dyn·s·cm⁻⁵)

In a US survey of providers treating CTEPH with medical targeted therapies instead of surgical referral, what was not one of the common reasons sited?

A. Better treatment options exist overseas
B. Patient refused
C. Deemed too sick for surgery
D. Comorbidity causing contraindication
US Physicians ‘self-screen’ patients prior to getting clinical evaluation for PEA

Reasons for not evaluating patients for PEA – Office-based US physicians only

- Improvement on drug treatment: 2
- Poor compliance: 2
- Unfamiliarity: 2
- Age: 3
- Insurance/Cost: 4
- Lack of evidence/poor experience/too risky: 5
- Access/resource: 8
- Pt refusal: 12
- Too sick/unstable/not fit for surgery/not candidates: 12
- Comorbidities/contraindications: 14

“I am not convinced that pulmonary endarterectomy is the best thing for my patients” US Pulm

“Surgical centers too far away” US Pulm

“Patients who did not want to see a surgeon, or who in my opinion too high risk for the procedure” US Haem

“Too sick, multi comorbidities, patient refuses” US Card

I. Preston, ERS 2012 meeting
Role of Medical Therapy in CTEPH

Unanswered Questions

Inoperable (defining operability)
Post-operative PH (defining significant PH)
Excess PH risk
Comorbidity
Patient refusal
PH with exercise
Early post-operative support… or wait-and-see

Long-term safety
Operability still questioned
Impact on referral practice
Role of Bridging Therapy?

Jensen KW, et al. Circulation ‘09. PH medical therapy = 4.5 months delay without effect on post-PTE outcomes


Nagaya N, et al. CHEST ‘03
Need for Bridging Therapy?

449 consecutive cases from Jan ‘09 – Jun ‘12
Pre-op PVR in excess of 1,500 dyn⋅s⋅cm⁻⁵ (18 cases)

Pre-op PVR 1,778 ± 293
Post-op PVR 374 ± 154

79% reduction in PVR
No deaths
But we also need long term follow-up

Kim NH, et al. ATS 2013 abstract
CTEPh: Operability

Operability

- Imaging
- Surgical experience
- Hemo-dynamics
- Patient factors

from Kim NH, 5th World Symposium on PH
### Operability Assessment

<table>
<thead>
<tr>
<th>Surgeon’s assessment</th>
<th>Non-operable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clot inaccessibility</td>
<td>118</td>
</tr>
<tr>
<td>PH severity and morphological lesions imbalance</td>
<td>25</td>
</tr>
<tr>
<td>PVR &gt; 1500 dsc-5</td>
<td>6</td>
</tr>
<tr>
<td>Age</td>
<td>5</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td>33</td>
</tr>
<tr>
<td>Other reasons</td>
<td>56</td>
</tr>
</tbody>
</table>

Pepke-Zaba J et al, Circulation 2011
**CTEPH:** Persistent/Recurrent PH

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Criteria</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayer, JTCVS 2011</td>
<td>386</td>
<td>mPAP&gt;25 end ICU</td>
<td>17%</td>
</tr>
<tr>
<td>Freed, JTCVS 2011</td>
<td>314</td>
<td>mPAP&gt;30 at 3 mo</td>
<td>31%</td>
</tr>
<tr>
<td>Madani, STS Meeting 2011</td>
<td>500</td>
<td>PVR&gt;500 end ICU</td>
<td>6%</td>
</tr>
<tr>
<td>Skoro-Sayer, Circulation 2009</td>
<td>103</td>
<td>PVR&gt;550 end ICU</td>
<td>14%</td>
</tr>
<tr>
<td>Corsico, AJRCCM 2008</td>
<td>157</td>
<td>PVR&gt;500 at 4y</td>
<td>24%</td>
</tr>
</tbody>
</table>

*No consensus on definition of PH post PEA*
CTEPH Diagnosis
Continue Lifelong Anticoagulation

Operability Assessment by CTEPH Team

Operable

Persistent symptomatic pulmonary hypertension

Pulmonary Endarterectomy

Non-operable

Recommend 2nd Opinion by experienced center

Targeted medical therapy

Referral for lung transplantation

PTPA?

Kim NH, et al. JACC 2013
Which patient benefited from PTE?
Summary

Pulmonary thrombo-endarterectomy is the treatment of choice in CTEPH.

All patients with CTEPH should be referred and evaluated for operability versus medical therapy by an experienced CTEPH team.

Riociguat is the only approved medical therapy for those with CTEPH deemed inoperable or with persistent PH following surgery.

Within CTEPH and medical therapy: still numerous unmet need and areas for investigative opportunities.
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