Therapeutic approaches in P(A)H and the new ESC Guidelines

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Disclosures

• Name of companies with which relevant financial relationship exists:
  – Actelion Pharmaceuticals
  – Bayer Schering
  – GlaxoSmithKline
  – Pfizer
  – United Therapeutics

• Nature of relationship:
  – Consultant
  – Honoraria
  – Advisory Board Member
PAH-specific therapies target the three signalling pathways involved in PAH

**Endothelin (ET) pathway**
- Pre-pro-ET $\rightarrow$ pro-ET
- ET-1
  - Vasoconstriction
  - Proliferation
- ET$_A$ ↔ ET$_B$
- Endothelin receptor antagonists (ERA)

**Nitric oxide (NO)-cGMP pathway**
- L-arginine $\rightarrow$ L-citrulline
- NO
  - Vasodilation
  - Anti-proliferation
- sGC stimulator $\uparrow$
- Phosphodiesterase 5 inhibitors (PDE-5i)

**Prostacyclin (PGI$_2$) pathway**
- Arachidonic acid $\rightarrow$ PGI$_2$
- PGI$_2$
  - Vasodilation
  - Anti-proliferation
- IP receptor $\uparrow$
- Prostacyclin receptor agonists

sGC: soluble guanylate cyclase

cAMP: cyclic adenosine monophosphate

cGMP: cyclic guanosine monophosphate

Guidelines for treatment of PAH are based on evidence from 29 RCTs with > 5,000 patients.

RCTs 1990-2005:
- Beraprost
- Bosentan
- Epoprostenol
- Sildenafil
- Treprostinil

1990:
- SUPER
- SERAPH

2005:
- STEP
- STRIDE2

2006:
- COMBI
- STRIDE2
- BREATHE5

2007:
- ARIES
- EARLY

2008:
- PACES
- PHIRST

2009:
- TRIUMPH
- IMATINIB
- Iversen

2010:
- FREEDOM C1
- SELEXIPAG
- IMATINIB
- Iversen

2011:
- FREEDOM M
- FREEDOM C2

2012:
- COMPASS-2
- AMBITION
- GRIPHON

2013:
- FREEDOM M

2014:
- SERAPHIN
- PATENT
- IMPRES
- FREEDOM C2

Monotherapy
Monotherapy and/or sequential combination
Initial combination

Freedom C

Freedom C2

IMPRES

SERAPHIN

PATENT

COMPASS 2 *

GRIPHON *

AMBITION *

No effect of oral treprostinil on 6MWD in FREEDOM C and FREEDOM C2

FREEDOM C

N=350 patients with PAH
On background therapy

FREEDOM C2

N=310 patients with PAH
On background therapy

Imatinib improved 6MWD in IMPRES

- \(N=202\) patients on background therapy

- No effect in delaying clinical worsening

- Safety issues (33\% vs 18\% completed, 8 subdural hematoma)

- Market approval application withdrawn

Riociguat improved 6MWD in PATENT-1

N=443 patients, both naive and on background therapy

Improvement in 2ary EP in the 2.5 mg tid group:
- NT Pro BNP
- WHO FC
- PVR
- Clinical worsening (n=13 events reported)

PATENT-1: Change in 6MWD for patients on background therapy (± 50%)

Patients on background therapy
(n = 131/60)
+34 m (95% CI: 11 - 56 m)

Mean change from baseline in 6MWD (m)

Riociguat
Placebo

SERAPHIN: event-driven trial with a composite morbidity and mortality EP

Time to 1st morbidity or mortality event

- All-cause death
  - OR
  - Atrial septostomy
  - OR
  - Lung transplantation
  - OR
  - Initiation of i.v. or s.c. prostanoids
  - OR
  - Other worsening of PAH

A decrease in 6MWD of at least 15%, confirmed by 2 tests on different days

Worsening of PAH symptoms, which must include either:
  - An increase in FC, or
  - Appearance or worsening of symptoms of right heart failure

Need for new PAH treatment(s):
  - Oral or inhaled prostanoids
  - Oral PDE-5 inhibitors
  - ERA after discontinuation of study drug
  - Intravenous diuretics

All events adjudicated by a blinded clinical events committee

6MWD: 6-minute walk distance; ERA: endothelin receptor antagonist; FC: functional class; PDE-5: phosphodiesterase-5

Macitentan delayed time to first event

- N=742 patients, both naive and on background therapy
- Randomisation 2:1 to macitentan (3 and 10 mg) vs PBO

Improvement in 2ary EP:
- 6MWD
- WHO FC
- NT Pro BNP
- PVR

SERAPHIN: effect of macitentan on primary endpoint in patients on PAH therapy (64%)

Risk reduction of primary endpoint event vs placebo
Macitentan 10 mg: 38%

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>Macitentan 10 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>154</td>
<td>134</td>
<td>119</td>
</tr>
<tr>
<td>154</td>
<td>122</td>
<td>106</td>
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<td>119</td>
<td>107</td>
<td>90</td>
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<td>107</td>
<td>97</td>
<td>80</td>
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<tr>
<td>97</td>
<td>80</td>
<td>40</td>
</tr>
<tr>
<td>53</td>
<td>40</td>
<td>10</td>
</tr>
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</table>

Treatment difference:
- Hazard ratio (HR) 0.62
- Log-rank p-value 0.009

NCT00323297: No additional benefit of sildenafil when added to bosentan

- N = 103 patients on background bosentan
- Primary endpoint: change in 6MWD at week 12
- Mean difference (final values) = -2.38 m
- p-value = 0.5802

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Sildenafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients analysed</td>
<td>53</td>
<td>50</td>
</tr>
<tr>
<td>Change from baseline at week 12 (n = 46,44)</td>
<td>17.42 ± 57.270</td>
<td>14.08 ± 63.679</td>
</tr>
<tr>
<td>Change from baseline at week 12 LOCF (n = 53,49)</td>
<td>14.08 ± 57.557</td>
<td>13.62 ± 60.950</td>
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LOCF: last observation carried forward
**COMPASS-2: no additional benefit of bosentan in patients on background sildenafil**

- Event-driven trial including around 350 patients on sildenafil

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Treatment effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to first morbidity/mortality event</td>
<td>HR = 0.831 (0.582, 1.187) (p = 0.2508)</td>
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<table>
<thead>
<tr>
<th>Secondary endpoints</th>
<th>Treatment effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in 6MWD to week 16</td>
<td>+21.8 (74)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>+13.0 (3.0, 23.0)</td>
</tr>
<tr>
<td>Median (95% CL)</td>
<td></td>
</tr>
<tr>
<td>Change in WHO FC to week 16</td>
<td>None</td>
</tr>
<tr>
<td>Time to death (all causes)</td>
<td>None</td>
</tr>
</tbody>
</table>

- Issues with sample size and duration (started in 2006)
- Improvement in 6MWD similar to other recent RCTs

Actelion press release, March 2013.
Phase III study with selexipag: GRIPHON

- N = 1156 patients
- Naive, or on background therapy (ERA, PDE5 inhibitor or both)
- Event-driven trial (composite EP of morbidity and mortality)
- Duration of treatment up to 4.3 years

80% were on background therapy
Decrease in risk of 39% (selexipag vs placebo, p<0.0001)
Efficacy across key subgroups

To compare 2 treatment strategies
initial combo (amb+tad) vs mono (amb or tad)

Primary objective: time to clinical failure

Secondary objectives:
- compare the changes in other clinical measures
- safety and tolerability
- 6MWD at peak and trough level
A randomised, multicentre study of first-line AMBrisentan and Tadalafil combination therapy in subjects with pulmonary arterial hypertensive disease.

**Trial Design**

- **Randomisation**: 2:1:1 to combination or monotherapy arm
- **Treatment Arms**:
  - Ambrisentan 10 mg o.d.
  - Tadalafil 40 mg o.d.
  - Tadalafil 40 mg o.d. + Ambrisentan 10 mg o.d.

- **Endpoints**:
  - Primary endpoint: Time to clinical failure
  - **n** = 614
  - **n** = 105 events

**Study Details**

- NCT01178073, www.clinicaltrials.gov
AMBITION primary endpoint: Time to first clinical failure event

Death (all cause)

Hospitalisation for worsening PAH
- non-elective hospitalisation (CW)
- lung transplantation
- atrial septostomy
- initiation of prostanoid therapy

Disease progression
- Decrease in 6MWD >15% vs base
  With FC III-IV (2 visits >14 days)

Unsatisfactory long-term response
- > 6 months on therapy
- Disease progression
  NYHA FC III-IV at 6 months

All events were adjudicated
**AMBITION: Primary and secondary endpoint analysis**

<table>
<thead>
<tr>
<th></th>
<th>Combination</th>
<th>Monotherapy pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of subjects</strong></td>
<td>253</td>
<td>247</td>
</tr>
<tr>
<td><strong>Number of subjects with first events (%)</strong></td>
<td>46 (18 %)</td>
<td>77 (31 %)</td>
</tr>
<tr>
<td><strong>Hazard ratio from Cox model</strong></td>
<td>0.502</td>
<td>95 percent CI: 0.348, 0.724</td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>0.0002</td>
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- All events contributed to reduce TtCF, driven by a reduction in hospitalizations (no effect on mortality)
- Initial combination improved NT Pro BNP, the % patients with satisfactory clinical response and 6MWD at W 24
- WHO FC and Borg dyspnea index were unchanged

Adapted from GSK press release - Galiè et al presented at ERS 2014 Abstract #2916 – Rubin et al presented at CHEST 2014
ESC guidelines 2004: First treatment algorithm

1. PAH, NYHA Class III/IV
   - Background Therapy and General Measures:
     - Oral anticoagulants (IIa C), Diuretics (I C), O₂ (IIa C), Digoxin (IIb C)
   - Expert Referral
     - Acute Vasoreactivity Test
       - Positive
         - Oral CCB (I C)
           - Sustained Response
             - Yes: Continue CCB
             - No
       - Negative
         - NYHA Class III
           - Endothelin R Antagonists
             - Bosentan (I A)
               - or
             - Prostanoid Analogue
               - Iloprost inh (IIa B), Treprostinil (IIa B), Beraprost (IIb B),
                 - or
             - Continuous IV prostacyclin
               - Epoprostenol (I A)
                 - or
               - PDE5 inhibitors
                 - Sildenafil (I A)
         - NYHA Class IV
           - Epoprostenol (I A)
             - Bosentan (IIa B)
             - Treprostinil (IIa B)
             - Iloprost IV (IIa C)
           - No improvement or deterioration: Combination Therapy (IIb C)
             - BAS (IIa C)
               - and/or
             - Lung Transplant (I C)
# 5th World Symposium on PH: Initial combination therapy for patients in FC III/IV

<table>
<thead>
<tr>
<th>Recommendation (Evidence*)</th>
<th>FC II</th>
<th>FC III</th>
<th>FC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (A or B)</td>
<td>Ambrisentan, Bosentan, <strong>Macitentan</strong>&lt;br&gt;Riociguat, Sildenafil, Tadalafil</td>
<td>Ambrisentan, Bosentan, <strong>Epoprostenol i.v.</strong>, Iloprost inhaled, <strong>Macitentan</strong>&lt;br&gt;Riociguat, Sildenafil, Tadalafil, Treprostinil s.c., inhaled†</td>
<td><strong>Epoprostenol i.v.</strong></td>
</tr>
<tr>
<td>IIA (C)</td>
<td>Iloprost i.v. †&lt;br&gt;Treprostinil i.v.</td>
<td>Ambrisentan, Bosentan, Iloprost inhaled and i.v.†&lt;br&gt;<strong>Macitentan</strong>, Riociguat, Sildenafil, Tadalafil, Treprostinil s.c., i.v., inhaled†</td>
<td></td>
</tr>
<tr>
<td>IIB (B)</td>
<td>Beraprost†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIB (C)</td>
<td>Initial combination therapy</td>
<td>Initial combination therapy</td>
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</table>

**Yellow:** Morbidity and mortality as primary endpoint in randomised controlled study or reduction in all-cause mortality (prospectively-defined)

*Level of evidence is based on the FC of the majority of the patients of the studies
†Approved only: by the FDA (treprostinil inhaled); in New Zealand (iloprost i.v.); in Japan and S. Korea (beraprost)

Expert consensus recommendations for sequential combination therapy have improved with increasing experience

Sequential combination therapy *may be considered* in patients who fail to show improvement or who deteriorate on a single drug (monotherapy)

Combination therapy *should be considered* in patients on monotherapy with ‘inadequate clinical response’

Evidence level: Ila-B

In case of inadequate clinical response, sequential therapy *is recommended*

Evidence level: I-A

In FC IV, initial combination should be considered

Evidence level: Ila-C

In FC III/IV patients initial combination therapy may be considered

Evidence level: IIb-C

Conclusions

• There is robust evidence supporting a strategy of sequential combination therapy in PAH.

• However, not all combinations appear to be associated with a similar benefit.

• It is unclear whether differences are due to the design of the RCTs, differences in populations, interaction between compound or true efficacy issues.

• If timing of sequential combination remains to be better understood, initial combination may be considered as standard of care.

• The jury is out to decide whether we should move from a drug-oriented to a strategy based treatment algorithm.