The role of intermittent use of Levosimendan in end stage HF

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Unrestricted grant from Orion Pharma (LevoRep Study)
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Change of hemodynamic Parameters within 24 hrs

- Change of CO: 23
d- Change of PCWP: -12
- Change of SV: 22
- Change of HR: 5, 7
- Change of sBP: -3

P-values:
- CO: P=0.048
- PCWP: P=0.26
- SV: P=0.22
- HR: P=0.002
- sBP: P=0.002
Pharmakokinetische profile

- Active Substance (t_{1/2} = 1h)
- Active Metabolite (t_{1/2} = \sim 80h)
- Efficacy up to 10-11 days
Sustained efficacy of Levosimendan

Levosimendan – LV-Funktion u. Biomarker

25 Patienten
NYHA III/IV
fortgeschrittene Herzinsuffizienz
zugewiesen zum Management
bei fortgeschrittener Herzinsuffizienz

5x seriell Levosimendan über 24h
In 3-wöchigen Abständen
2:1 Randomisierung

Effects of serial levosimendan infusions on left ventricular performance and plasma biomarkers of myocardial injury and neurohormonal And immune activation in patients with advanced heart failure Parissis et al Heart 2006
No interaction with β-blockers

\[ \Delta \text{CO} \quad \Delta \text{PCWP} \]

<table>
<thead>
<tr>
<th>Levosimendan</th>
<th>Dobutamin</th>
</tr>
</thead>
<tbody>
<tr>
<td>without β-Blocker</td>
<td>without β-Blocker</td>
</tr>
<tr>
<td>with β-Blocker</td>
<td>with β-Blocker</td>
</tr>
</tbody>
</table>

- **CO (l/min)**
  - Levosimendan: β- β+  
  - Dobutamin: β- β+  

- **PCWP (mmHg)**
  - Levosimendan: β- β+  
  - Dobutamin: β- β+  

- **Statistical Significance**
  - p = 0.01  
  - p = 0.03
<table>
<thead>
<tr>
<th>Levo-REP</th>
<th>Lion-Heart</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA III or IV &gt; 3 months</td>
<td>• NYHA III/IV &gt; 4 week</td>
</tr>
<tr>
<td>LVEF &lt;35%</td>
<td>• LVEF &lt;35%</td>
</tr>
<tr>
<td>Six-minute walk test &lt;350 m</td>
<td>• Episode of pulmonary or systemic congestion requiring i.v. vasoactives within 12 months</td>
</tr>
<tr>
<td>Optimal neurohormonal background therapy</td>
<td>• Optimal neurohormonal background therapy</td>
</tr>
</tbody>
</table>
LevoRep – study protocol

Outpatient management, 6h administration at 0.2 µg/kg/min every 2 weeks

Max. 1 week

Screening

Randomization

Baseline

1. Cycle
2. Cycle
3. Cycle
4. Cycle

16 weeks

Long term Follow Up

Levosimendan
0.2ug/kg/min for 6 h

2 weeks

Short term Follow up

2- weeks Follow Up

6 weeks

Treatment

Altenberger, Poelzl, et al. Euro J Heart Fail 2013
LION-HEART – Study Protocol

Screening
1 week

Outpatient Therapy Follow-up
3 months

Levosimendan
0.2μg/Kg/min for 6 hours every 2 weeks

Placebo
0.2μg/Kg/min for 6 hours every 2 weeks

Arrhythmia Evaluation
(24 h Holter Monitoring)

Primary End-Point
Changes in NT-proBNP
Comparing AUC of NT-proBNP from pre and post 24h infusion levels of NT-proBNP)

PRO Week 13

PRO Week 25

End of Study
Primary endpoint
(Improvements in six min walk test ≥20% and KCCQ clinical summary score ≥15%)

Altenberger, Poelzl, et al. Euro J Heart Fail 2013
LION-HEART – Study Results

Δ% Change of NT-proBNP

- Mean±SEM % of change in NT-proBNP by Treatment Group

- Placebo
- Levosimendan

- p-value < 0.001
LevoRep – results

Drop in NT-proBNP by ≥30%

- **Levosimendan**
  - 8 wks: 45.5%
  - 24 wks: 17.8%
- **Placebo**
  - 8 wks: 23.3%
  - 24 wks: 15.4%

*p = 0.006*

*p = 0.41*
Lion-Heart: patient outcome

**Placebo event rate about 80 %**

**Effect size with levosimendan > 50 %**

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Levosimendan</th>
<th>p-value</th>
<th>HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Failure Hospitalization</td>
<td>14 (67%)</td>
<td>11 (23%)</td>
<td>0.002</td>
<td>0.25 (0.11-0.55)</td>
</tr>
<tr>
<td>All-cause Death</td>
<td>7 (33%)</td>
<td>14 (29%)</td>
<td>0.951</td>
<td>0.85 (0.34-2.12)</td>
</tr>
<tr>
<td>All-cause Death or Heart Failure Hospitalization</td>
<td>17 (81%)</td>
<td>23 (48%)</td>
<td>0.022</td>
<td>0.39 (0.21-0.74)</td>
</tr>
</tbody>
</table>

*Cox Proportional Hazards Models (time to first event)*

**KM curves**
Levo-REP: patient outcome*

Event-free survival = freedom from death, heart transplantation, or acute heart failure during the first 180 days after randomization

* Placebo event rate about 35%
* Effect size with levosimendan about 50%

*) Event free survival = freedom from death, heart transplantation, or acute heart failure during the first 180 days after randomization
Survival benefit with pulsed administration of levosimendan

**Meta-analysis** on trials with levosimendan vs placebo, dobutamine or prostaglandins

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Levosimendan</th>
<th>Control</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Altenberger J 2013</td>
<td>1</td>
<td>63</td>
<td>4</td>
<td>57</td>
</tr>
<tr>
<td>Berger R 2007</td>
<td>6</td>
<td>39</td>
<td>7</td>
<td>36</td>
</tr>
<tr>
<td>Bonios MJ 2012</td>
<td>14</td>
<td>42</td>
<td>8</td>
<td>21</td>
</tr>
<tr>
<td>Comin-Colet 2015</td>
<td>14</td>
<td>48</td>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td>Kleber FX 2009</td>
<td>0</td>
<td>18</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Malfatto G MD 2012</td>
<td>4</td>
<td>22</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Mavrogeni S 2007</td>
<td>2</td>
<td>25</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>257</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>181</strong></td>
<td><strong>54 [0.32, 0.91]</strong></td>
</tr>
</tbody>
</table>

Total events 41

Heterogeneity: Chi² = 4.28; df = 6 (p = 0.64); I² = 0%

Test for overall effect: Z = 2.32 (p = 0.02)
Effect of dobutamine or high-dose dopamine compared to control or placebo on mortality

*Thackray S et al. Eur J Heart Fail 2002;4:515-529*
LION-HEART – Study Results - Safety and Tolerability

Safety analysis #2: Mean and standard deviation of the differences from baseline to visit 7 (3 months) in blood biomarkers of renal and liver function

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Placebo n=21</th>
<th>Levosimendan n=48</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine, mg/dL</td>
<td>&lt;0.1 (0.4)</td>
<td>-0.1 (0.3)</td>
<td>0.428</td>
</tr>
<tr>
<td>AST, UI/L</td>
<td>4.1 (10.7)</td>
<td>-2.3 (6.7)</td>
<td>0.029</td>
</tr>
<tr>
<td>ALT, UI/L</td>
<td>3.5 (18.4)</td>
<td>-0.2 (8.3)</td>
<td>0.233</td>
</tr>
</tbody>
</table>

% of patients receiving all planned infusions

% of patients needing reduction or interruption of the infusion due to significant hypotension (SBP<80 mmHg or symptoms)
Δ Syst. BP (mmHg)

Δ Heart Rate (bpm)

p = 0.01

1,2±6

p = 0.02

-1,3±4

-7,1±14

Levosimendan (n=232)  Placebo (n=214)

Altenberger, Poelzl, et al. Euro J Heart Fail 2013
## LevoRep – adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>Levosimendan</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients / applications</td>
<td>63 / 232</td>
<td>57 / 214</td>
<td></td>
</tr>
<tr>
<td>Hypotension (&lt;80mmHg), (%)</td>
<td>15 (24)</td>
<td>8 (14)</td>
<td>p = 0.25</td>
</tr>
<tr>
<td>measures taken (%)</td>
<td>12 (19)</td>
<td>6 (11)</td>
<td></td>
</tr>
<tr>
<td>dose reduction</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>interim stop of infusion</td>
<td>7</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>permanent stop of infusion</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>fluid administration</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>vasopressor w/o stop of inf.</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Tachycardia (&gt; 120bpm)</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>New onset atrial fibrillation</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Ventricular tachycardia, non-sustained</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total (%)</td>
<td>16 (25)</td>
<td>9 (16)</td>
<td>p = 0.26</td>
</tr>
<tr>
<td>Completed infusion w/o AE (%)</td>
<td>212 (91)</td>
<td>201 (94)</td>
<td></td>
</tr>
</tbody>
</table>
Intermittent levosimendan in end-stage HF: which patient?

- Severe systolic dysfunction (LVEF < 35%)
- NYHA IIIb-IV a/o INTERMACS levels 4,5,6
- Repeat hospitalisation or emergency department visits (≥ 2 in the past year)
- All of the above despite optimal treatment for heart failure
Intermittent levosimendan in end-stage HF: which dosage?

• 0.5 – 0.2 mcg/kg/min for 6 to 24 hrs.

• No bolus!

• Intervals: weekly – bi-weekly – monthly
Intermittent levosimendan in end-stage HF: measures of caution?

- Systol. BP ≥ 85 -100 mmHg
- eGFR ≥ 30 ml/min/1.73 qm
- Potassium ≥ 3.5 mg/dl
- No hypovolemia – no diuretics before infusion of levosimendan
Intermittent levosimendan in end-stage HF: monitoring?

- RR and HR control
- Control of renal function and electrolytes
- Outpatient setting possible
Intermittent use of levosimendan in end-stage HF

- well documented
- effective
- save
- pooled-data analysis of LevoRep and LionHeart planned
- large prospective randomized trial under discussion