TRV120027, a Novel β-Arrestin Biased Ligand at the Angiotensin II Type I Receptor, Unloads the Heart and Maintains Renal Function When Added to Furosemide in Experimental Heart Failure

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Disclosures

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• DG Soergel, JD Violin, and MW Lark are employees of Trevena, Inc.
Background

• Acute decompensated heart failure (HF) is associated with high mortality and morbidity, including frequent rehospitalization.

• Despite advances in the treatment of chronic HF, the treatment of acute decompensated HF remains largely empirical.

• Loop diuretics are frequently used in HF but they can result in diuretic resistance and worsening renal function, which are associated with adverse outcomes.¹,²

• Novel innovative therapies are urgently needed.

¹Felker GM et al, NEJM 2011;364:797-805
²Forman DE et al, JACC 2004;43:61-7
Angiotensin II

AT1R

Vasoconstriction
Glomerular filtration ↓
Na⁺ reabsorption ↑
Angiotensin II

- Vasoconstriction
- Glomerular filtration ↓
- Na⁺ reabsorption ↑

- Balanced vasodilation
- Cardiac performance ↑
- Renal perfusion ↑
AT1 receptor blocker

Vasoconstriction
Glomerular filtration ↓
Na+ reabsorption ↑

Balanced vasodilation
Cardiac performance ↑
Renal perfusion ↑
TRV120027

AT1R

β-arr

Vasoconstriction
Glomerular filtration ↓
Na+ reabsorption ↑

Balanced vasodilation
Cardiac performance ↑
Renal perfusion ↑
TRV120027

• A β-arrestin biased ligand at the AT1R

• Vasodilation and increased cardiac performance in rats \(^1\)

• In canines with experimental HF \(^2\):
  • Vasodilation, reduction in MAP
  • Increased cardiac output
  • Maintained sodium excretion and GFR
  • Blood pressure reductions were rapidly reversible

\(^1\)Violin JD et al, J Pharm Exp Ther 2010:335:572-9
\(^2\)Boerrigter G et al, Circ HF 2011, Epub 8/2011
Hypothesis

We hypothesized that in experimental HF TRV120027 with its unique pharmacology would have beneficial cardiac unloading actions when added to furosemide while preserving renal function.
Methods

• We assessed the acute cardiorenal and humoral actions of TRV120027 and furosemide in a canine model of HF

• HF was induced by tachypacing (240 beats/min for 10 days), resulting in a HF phenotype with decreased cardiac output, vasoconstriction, sodium retention, and neurohumoral activation

• An acute study under general anesthesia was done on day 11 of pacing

• Surgical preparation included a Swan-Ganz catheter, a catheter in the left ureter, and an electromagnetic flow probe on the left renal artery to measure renal blood flow
Acute Protocol

Inulin bolus

Base-line

Equilibration

C1

60’  30’

Inulin 1 mL/min

Saline 0.5 mL/min

Saline 0.5 mL/min
Acute Protocol

Inulin bolus

Base-line

Equilibration

C1

C2

C3

60'

30'

15'

30'

15'

30'

Inulin 1 mL/min

Saline 0.5 mL/min

Saline 0.5 mL/min

Furosemide 1 mg/kg/h

0.3

1.5

µg/kg/min

TRV120027
Acute Protocol

Inulin bolus

Equilibration

Baseline

C1

C2

C3

Washout

C4

Post infusion

60' 30' 15' 30' 15' 30' 30' 30'

Inulin 1 mL/min

Saline 0.5 mL/min

Furosemide 1 mg/kg/h

Saline

0.3 µg/kg/min

TRV120027

Saline
Acute Protocol

Inulin bolus

Equilibration

Baseline

C1

60'

30'

C2

15'

30'

15'

C3

30'

Washout

C4

30'

30'

Post infusion

Inulin 1 mL/min

Saline 0.5 mL/min

Furosemide 1 mg/kg/h

Saline

Saline

Saline

Saline
Methods

• Neurohormones were measured by radioimmunoassay, glomerular filtration rate by inulin clearance

• **Within-group changes** were analyzed with 1-way analysis of variance for repeated measurements with post-hoc Dunnett’s test (or Friedman’s test for not normally distributed data)

• Differences **between groups** were analyzed by comparing the changes from baseline with unpaired t-test (or Mann-Whitney U-test for not normally distributed data)

• Statistical significance was accepted at $p<0.05$
Results
TRV120027 reduces cardiac afterload

- **Δ MAP (mmHg)**
  - C1:ypsy
  - C2: 0
  - C3: -10
  - C4: -20

- **Δ CO (L/min)**
  - C1: 0.2
  - C2: 0.1
  - C3: 0
  - C4: -0.1

* p<0.05 vs. respective baseline
# p<0.05 between groups
TRV120027 reduces cardiac preload

\[ \Delta \text{RAP (mmHg)} \]

\[ \Delta \text{PCWP (mmHg)} \]

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<th>C1</th>
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<tr>
<td>0</td>
<td>-1</td>
<td>-2</td>
<td>-3</td>
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\[ \Delta \text{RAP (mmHg)} \]

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<tr>
<td>2</td>
<td>-2</td>
<td>-4</td>
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* \( p < 0.05 \) vs. respective baseline
# \( p < 0.05 \) between groups

Furosemide + saline
Furosemide + TRV120027
TRV120027 reduces systemic and pulmonary vascular resistances

Δ SVR (mmHg·L⁻¹·min)

Δ PVR (mmHg·L⁻¹·min)

Furosemide + saline
Furosemide + TRV120027

* p<0.05 vs. respective baseline
# p<0.05 between groups
Renal blood flow and glomerular filtration rate are preserved with TRV120027.

- Furosemide + saline
- Furosemide + TRV120027

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<td>Δ RBF (ml/min)</td>
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<td>Δ GFR (mL/min)</td>
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* p<0.05 vs. respective baseline
# p<0.05 between groups
Renal excretory function is preserved during and enhanced after TRV120027 infusion.

**Δ UVolR (mL/min)**

- C1
- C2
- C3
- C4

**Δ UNaV (mL/min)**

- C1
- C2
- C3
- C4

* p<0.05 vs. respective baseline
# p<0.05 between groups

- **Furosemide + saline**
- **Furosemide + TRV120027**
Reduced distal fractional Na\(^+\) reabsorption in post-infusion may be related to aldosterone suppression.
TRV120027 reduces ANP, consistent with greater cardiac unloading.

![Graph showing the change in ANP (Δ ANP) levels over time with different treatments.]

- Furosemide + saline
- Furosemide + TRV120027

* p<0.05 vs. respective baseline
# p<0.05 between groups
Summary

Addition of TRV120027 to furosemide resulted in

• potent cardiac unloading actions with reduction in systemic and pulmonary vascular resistances
• maintained renal blood flow and GFR
• maintained urine flow and urinary sodium excretion during drug infusion but augmented sodium excretion and diuresis in the post-infusion clearance
• trend for reduced aldosterone, consistent with reduced DFRNa in the post-infusion clearance
• significant reduction in plasma ANP consistent with cardiac unloading
Conclusions

• When added to furosemide, TRV120027 demonstrated potent cardiac unloading actions while preserving renal function

• Thus, the previously reported cardiorenal actions of TRV120027 are preserved when given with furosemide\(^1\)

• Further studies are required to assess whether the apparent enhanced renal action in the post-infusion clearance is due to a renal protective or enhancing action of TRV120027 and whether this could translate into better renal outcomes in HF patients

• The unique vascular, cardiac, and renal pharmacology of TRV120027 supports further studies in human HF

\(^1\) Boerrigter G et al, Circ HF 2011, Epub 8/2011