Disclosures

Consultancy: Galecto Biotech, Gilde Healthcare, Caldan Therapeutics, Cypralis, Arix Bioscience, Ferring Pharmaceuticals

Scientific Advisory Boards: Novartis, Galecto Biotech, NIHR Leeds Medtech and In-vitro Diagnostic Cooperative (MIC)

Research funding: GlaxoSmithKline, Intercept Pharmaceuticals, Novartis (IIT)
Acute kidney injury in cirrhosis

Affects up to 50% of hospitalized patients with cirrhosis

Increases mortality by 7-fold compared to patients without AKI

Median survival of hepatorenal syndrome (AKI-HRS) ~1 month

Diagnosis is challenging (serum creatinine is a poor proxy of renal health in cirrhosis; no specific diagnostic tests; AKI causes co-exist)

Response to vasoconstrictor therapy in AKI-HRS is variable, sub-optimal (~40%), unpredictable and potentially hazardous
**Pathophysiology of AKI-HRS**

Central feature of HRS is intense **renal vasoconstriction** (cortex)

- **Systemic inflammation**
- **Microvascular dysfunction**
- **Chronic kidney disease**

The kidneys are potentially salvageable

**HRS**

**non HRS**
AKI in cirrhosis - a new approach to improve outcomes

- Early assessment of prognosis
- Predict and monitor terlipressin response (accurate phenotyping)

New biomarkers – blood, urine, imaging

Alternative treatments (e.g. serelaxin)
AKI biomarker studies

- Chief Scientist Office (CSO) Catalytic Grant (Ref: CGA/16/45): ‘Prognostic Biomarkers for Acute Kidney Injury in Liver Cirrhosis’
  - n=53; pKIM-1, FeNa, uL-FABP, uPCR, uKIM-1 on admission

- Edinburgh and Lothians Health Foundation Research Grant (Ref: SO7074): ‘Superior markers of renal dysfunction in patients admitted for liver transplant assessment could improve both short and long term outcomes’
  - n=?; pre-transplant biofluid biomarkers, renal MRI, impedance cardiography, aortic pulse wave velocity, retinal optical coherence tomography

- Sir Jules Thorn application (unsuccessful) – MRI to phenotype AKI, stratify/monitor terlipressin response – resubmission ?NIHR EME
Multiparametric renal MRI
A composite biomarker of kidney microstructure and haemodynamics

↓ cortical perfusion is a landmark feature of HRS

Progressive ↓ in cirrhosis; can monitor response to vasoactive drugs

↓ cortical $T_1$ linked to disease severity, adverse outcomes

↑ $T_1$ in CKD

Reflects degree of intra-renal hypoxia and progression of AKI

A single, <30 minute, non-contrast, free-breathing MRI scan

Cox E et al., Front Physiol 2017; Bradley C et al., J Hepatol 2018; Snowdon V et al., PLoS Med 2017
Recombinant human relaxin-2 (serelaxin)
Anti-fibrotic and vasoactive effects in preclinical models

- ↓ portal pressure
- ↑ intrahepatic NO
- ↑ / ↔ hepatic perfusion
- ↔ mean arterial BP

↓ HSC-myofibroblast activation, contractility

↑ IHVR
↓ NO

↑ / ↔ hepatic perfusion
↔ mean arterial BP

↑ matrix metalloproteinases
↓ fibrosis

↓ endothelial dysfunction
↓ renal vascular resistance
↑ renal blood flow
↑ GFR
↔ mean arterial BP

Fallowfield JA et al., Hepatology 2014
Snowdon VK et al., PLoS Medicine 2017
McBride A et al., Sci Rep 2017
Serelaxin: renal and hepatic haemodynamic data
Novartis sponsored Phase II Trial (NCT01640964)

Percent changes in blood flow from baseline (95% CI)

<table>
<thead>
<tr>
<th>VESSEL</th>
<th>Total (left + right) renal artery</th>
<th>Superior abdominal aorta</th>
<th>Superior mesenteric artery</th>
<th>Portal vein</th>
<th>Hepatic artery</th>
<th>Total liver blood flow (portal vein + hepatic artery)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serelaxin</td>
<td>+ 65.4 (40.0, 95.5)</td>
<td>+ 7.8 (1.8, 14.2)</td>
<td>– 1.5 (–8.0, 18.1)</td>
<td>– 11.9 (–22.1, –0.3)</td>
<td>+ 18.0 (3.4, 44.2)</td>
<td>– 0.54 (-7.3, 7.8)</td>
</tr>
<tr>
<td>Terlipressin</td>
<td>+ 13.5 (3.3, 33.3)</td>
<td>– 18.8 (–23.6, –13.7)</td>
<td>– 36.9 (–45.0, –27.6)</td>
<td>– 40.0 (–57.2, –16.1)</td>
<td>– 7.1 (–32.7, 28.1)</td>
<td>– 34.7 (-13.3, -50.8)</td>
</tr>
</tbody>
</table>

- Link between improved renal haemodynamics and renal function has not yet been established.

Snowdon V et al., PLoS Medicine 2017
Serelaxin: portal pressure effect in TIPSS patients
Novartis sponsored Phase II Trial (NCT01640964)

- Small exploratory sub-study \((n=6)\)
  - TIPSS portogram ✓
  - PPG (PVP-IVCP) >5mm Hg ✓
  - Serelaxin i.v. infusion with PVP monitoring for 120 min
- Serelaxin was well tolerated in advanced cirrhosis
- Rapid and potentially clinically significant ↓ in PP

<table>
<thead>
<tr>
<th>Time point (min) after initiation of serelaxin</th>
<th>PPG</th>
<th>PVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥120 ((n=6))</td>
<td>31.3</td>
<td>25.2</td>
</tr>
<tr>
<td>30 ((n=6))</td>
<td>7.2</td>
<td>25.2</td>
</tr>
<tr>
<td>60 ((n=6))</td>
<td>15.5</td>
<td>25.2</td>
</tr>
<tr>
<td>120 ((n=6))</td>
<td>15.5</td>
<td>25.2</td>
</tr>
<tr>
<td>135 ((n=5))</td>
<td>33.9</td>
<td>33.9</td>
</tr>
</tbody>
</table>

% reduction geometric mean (95% CI)

- Lachlan NJ et al., AASLD 2016
Serelaxin To Lower Portal Pressure (STOPP)
Novartis funded Investigator Initiated Trial (NCT02669875)

- Randomised, double-blind, placebo-controlled, Phase II, single centre study
- Male and female adult patients with cirrhosis and CSPH (HVPG >10mmHg) at baseline
- n=9 serelaxin, n=2 placebo before drug supply expired (target n=20)
- Studied the effects of serelaxin on portal and systemic haemodynamics (ICG clearance, impedance cardiography, APWV)
- Data in submission
- Novartis have closed all global serelaxin programmes
Serelaxin attenuates renal inflammation and fibrosis in a mouse model of dilated cardiomyopathy

Beverly Giam, Po-Yin Chu, Sanjaya Kuruppu, A. Ian Smith, Duncan Horlock, Aishwarya Murali, Helen Kiriazis, Xiao-Jun Du, David M. Kaye, Niwanthi W. Rajapakse

First published: 12 October 2018 | https://doi.org/10.1113/EP087189

Serelaxin induces Notch1 signaling and alleviates hepatocellular damage in orthotopic liver transplantation

Shoichi Kageyama, Kojiro Nakamura, Bilbo Ke, Ronald W. Busuttil, Jerzy W. Kupiec-Weglinski

First published: 21 February 2018 | https://doi.org/10.1111/ajt.14706 | Cited by: 6

Effects of human relaxin-2 (serelaxin) on hypoxic pulmonary vasoconstriction during acute hypoxia in a sheep model

Dong Wang1, Yuphan Luo1, Komuraiah Myakala1, David J. Orlicky2, Evgenia Dobrinskikh2, Xiaoxin Wang2 & Moshe Levi2

Received: 5 June 2017
Accepted: 26 July 2017

Effects of serelaxin on renal microcirculation in rats under control and high-angiotensin environments

Wenjian Shao, Carla B. Rosales, Camila Gonzalez, Minofa C. Prieto, and L. Gabriel Navar

Department of Physiology, Tulane Hypertension and Renal Center of Excellence, Tulane University School of Medicine, New Orleans, Louisiana
B7-33 replicates the vasoprotective functions of human relaxin-2 (serelaxin)

Sarah A. Marshall, Kelly O'Sullivan, Hooi Hooi Ng, Ross A.D. Bathgate, Laura J. Parry, Mohammed Akhter Hossain, Chen Huei Leo, Ashely Woods, and Weijun Shen

Calibre at the Scripps Research Institute, 11119 North Torrey Pines Road, La Jolla, California 92037, United States

Supporting Information