Novel Therapies in Alcoholic Hepatitis

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Focus on key elements of the pathogenesis of alcoholic hepatitis

• Inflammatory cascade and innate immune activation
  – a demarcating feature of severe AH compared to mild to moderate alcoholic liver disease

• Gut integrity
  – that is significantly altered in alcoholic hepatitis allowing pathogen-associated molecular patterns (PAMPs) to enter the liver and systemic circulation and induce innate immune activation,

• Cell survival and death pathways
  – that contribute to liver dysfunction and the release of damage-associated molecular patterns (DAMPs) that further fuel inflammation.
Hypotheses

- The syndrome of acute alcoholic hepatitis (AAH) results from severe inflammation and dysregulated cytokines.

- Gut derived endotoxins and other bacterial products that trigger inflammation are a consequence of increased permeability and altered gut barrier function.

- Compounds that improve the gut barrier function (both in moderate and severe disease) AND reduce the associated inflammation (severe disease) AND prevent the development of hepatorenal syndrome and other organ failure (severe disease) have utility in the treatment of severe AAH.
Two Multicenter Pilot Clinical Trials in AH

Identify Potential Subjects with Acute Alcoholic Hepatitis

Stratify for Disease Severity

MELD <20

MILD-MODERATE AH

MELD 20-31 + DF>32

MELD >31 + DF>32

SEVERE AH

Novel Treatment

Novel Treatment

Observational study
Aim #1

Aim 1: Evaluation of the effects of corticosteroids versus a combination of interleukin-1 receptor antagonist plus pentoxifylline plus zinc supplements in patients with MELD > 21.

IL-1 receptor antagonist attenuates ASH and progression of liver damage in mice
Multicenter randomized double-blind pilot study in severe alcoholic hepatitis

SEVERE AH

- Primary outcome: 6 month mortality
- Secondary outcomes
  - 30, 90 day mortality
  - changes in MELD at 30, 90, 180 days
  - changes in gut mucosal integrity
  - endotoxin levels & cytokine profiles

**MELD 20-31 + DF>32**

Prednisone (n = 65)

**MELD >31 + DF>32**

IL-1RA * + pentoxiphylline + zinc (n = 65)

* IL-1RA: Interleukin-1 Receptor Antagonist
Aim 2: Evaluation of the effects of probiotic supplements versus standard care on improvement in MELD score and gut mucosal integrity in patients with MELD < 21.

Probiotics modulate intestinal integrity/mucins and liver injury in human AH

McClain et al (unpublished data)
Multicenter randomized double-blind pilot study in moderate alcoholic hepatitis

MILD-MODERATE AH

- MELD <20

- Placebo (n = 68)
- Probiotic (n = 68)

- Primary outcome: 30 day change in MELD
- Secondary outcomes
  - 90, 180 day change in MELD
  - Changes in gut mucosal integrity
  - Endotoxin levels & cytokine profiles
UO1 Clinical Trial

Specific Aims

Aim 1: Evaluation of the effects of corticosteroids versus a combination of interleukin-1 inhibitor plus pentoxifylline plus zinc supplements in patients with MELD > 21.

Aim 2: Evaluation of the effects of probiotic supplements versus standard care on improvement in MELD score and gut mucosal integrity in patients with MELD < 21.

Aim 3: Develop new clinical trials for patients with alcoholic hepatitis using lead compounds identified by the translational science components of the U01 consortium.

Aim 4: Create a data and tissue biorepository
Synergy between the UO1 components
UO1-Translational
Novel Therapies in Alcoholic Hepatitis

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Specific Aim 1

• Evaluate the role of probiotics in modulating intestinal integrity/mucins and liver injury in animal models and in human AH.
Human Alcoholic Endotoxemia

49 alcoholics without clinical liver disease undergoing alcohol abuse treatment at NIH
Probiotic (LGG) treatment reduces endotoxin and attenuates inflammation/liver injury.
Alcohol effects microbiota over time and LGG attenuates this.
Alcohol alters gut microbiota, fecal pH/metabolomics

Fecal pH

Time, Week

Gram -

OTU

Alcaligenes

Succinic acid positively regulates HIF
LGG-supernatant Pretreatment Reduced Acute-Alcohol-Induced Hepatic Steatosis and Liver Injury

**Cramp**

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<th>Control</th>
<th>EtOH</th>
<th>EtOH+LGG-s</th>
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**Serum LPS**

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**TNF**

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**H&E and Oil Red O Staining**

**TG**

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<td>TG, mg/g liver</td>
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**Serum ALT**

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<td>Serum ALT, U/L</td>
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Lipids (short-chain fatty acids)
Alcohol modifies fecal metabolites including SCFAs

SCFA:
- Fermentation product of specific bacteria
- Can act through G protein-coupled receptors
- Butyrate inhibits HDACs

- ↓ SCFA
- Altered bile acids
- ↓ BCAA
Tributyrin attenuates endotoxin and Hepatic Steatosis

Tributyrin = Stable, rapidly absorbed prodrug of butyric acid

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**Endotoxin**

- **Control**
- **Alcohol**
- **Tributyrin**
- **Alcohol + Tributyrin**

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**Hepatic Triglycerides**

- **Controls**
- **Alcohol**
- **Tributyrin**
- **Alcohol + Tributyrin**
**Effects of Dietary Fat and EtOH on the Bacterial Diversity**

**Actinobacteria Phylum**

- **Gram +, p <0.001**

**Proteobacteria Phylum**

- **Gram -, p <0.001**

Kirpich et al., unpublished data
Enroll Patients!
Zinc Sulfate for Alcoholic Cirrhosis (ZAC) Clinical Trial - Interim Analysis of Liver Injury/Inflammation Biomarkers

Department of Medicine, Division of Gastroenterology, Hepatology and Nutrition, Department of Pharmacology and Toxicology, Alcohol Research Center, Louisville VA Medical Center, University of Louisville, Louisville, KY 40202.
Start:
AC  n=22

Zinc x 3 months
n=12

Placebo 3 months
n=10

Controls  n=10
TGF-β

* $P = 0.004$

pg/ml

Months on (220mg) Zinc
Child-Pugh

* $P = 0.004$

**Months on (220mg) Zinc**

**Child-Pugh Score**

- 10
- 9
- 8
- 7
- 6
- 5
- 4
Enroll Patients!