Management of alcoholic hepatitis: Implications for options beyond the STOPAH study

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Progression of alcoholic liver disease

Normal liver

Fatty liver

10-35%

10-35%

90-100%

Alcoholic hepatitis (steatohepatitis)

Cirrhosis

Hepatocellular cancer

Upto 70%

8-20%
Alcoholic Fatty Liver

- microvesicular fat
- macrovesicular fat
“foamy hepatocytes”

Acute Alcoholic Hepatitis

- Mallory body and neutrophils
- Fatty change
- Sinusoidal collagen deposition
A Histologic Scoring System for Prognosis of Patients with Alcoholic Hepatitis
A Histologic Scoring System for Prognosis of Patients with Alcoholic Hepatitis: Three-month survival probability of patients with AH

**A**

![Survival Curve A](image)

**AHHS (points)**

- Mild (0-3): 30, 29, 29, 29
- Moderate (4-5): 80, 75, 68, 65
- Severe (6-9): 107, 68, 55, 52

**Log Rank Test:** P < .0001
- Multiple comparison correction
  - Mild vs Moderate: P = .04
  - Moderate vs Severe: P < .0001

**B**

![Survival Curve B](image)

**AHHS (points)**

- Mild (0-3): 17, 17, 17, 17
- Moderate (4-5): 24, 22, 21, 20
- Severe (6-9): 68, 57, 48, 44

**Log Rank Test:** P = .008
- Multiple comparison correction
  - Mild vs Moderate: P = .08
  - Moderate vs Severe: P = .007

Altamirano et al
Gastroenterology, vol. 146, no. 5, pp. 1231-9.e1-6
Clinical Progression of ALD

Alcoholic

- Fatty liver
- Steatohepatitis
- Fibrosis
- Cirrhosis

Acute alcoholic hepatitis

ALD

cirrhosis

HCC

Years

10
20
30
Prognosis
Acute Alcoholic Hepatitis

• Acute mortality (50% die within one month)
  – Hepatic encephalopathy
  – Coagulopathy (PT prolongation > 6 seconds over control)
  – Bilirubin > 8mg/dl
  – Decreased albumin < 2.5 g/dl
  – Creatinine > 2mg/dl
  – Maddrey discriminant factor > 90 (4.6 x PT + bilirubin)
  – Increase in serum TNFα correlates with severity
Serum TNFα levels correlate with survival in alcoholic hepatitis

<table>
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<tr>
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<th>Detectable TNF at any time</th>
<th>No detectable TNF at any time</th>
<th>P value</th>
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<td>Dead</td>
<td>14</td>
<td>0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Alive</td>
<td>3</td>
<td>6</td>
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Inflammation in alcoholic liver disease

- Ethanol
  - ↑ LPS + other PAMPs
  - gut
  - ↑ bacterial overgrowth
  - ↑ gut permeability

- Liver lobules
- ROS
- Mitochondrial damage

- Inflammatory cells
  - Kupffer cells
  - Monocytes
  - T-cells
  - NKT cells
  - Neutrophils
- Activation

- MCP-1, MIP-1
- RANTES
- TNFα
- IL-1β
- IL-6
- Recruitment

- Liver injury
- Bone marrow
Alcoholic Hepatitis

Modified from FEBS Letters 2007, 581:3723
Biological Activities of Cytokines in Alcoholic Liver Disease

- Encephalopathy
- Fever
- Anorexia
- Energy Expenditure
- Triglycerides
- Liver Injury
- Collagen Deposition
- Altered Amino Acid Metabolism
- Muscle Wasting
- Gut Permeability
- Osteoporosis
- Altered Mineral Metabolism
- Zinc
- Hypoalbuminemia
- Endothelial Permeability with Edema Formation
Probability of acute kidney injury (AKI) development according to the presence of systemic inflammatory response syndrome (SIRS) at admission in alcoholic hepatitis patients.
Management of Alcoholic Hepatitis

Mathurin and Lucey
Management of Alcoholic Hepatitis

Candidates for treatment (corticosteroids or pentoxifylline) need to fulfill the following criteria:

- Recent onset of jaundice (less than 3 months)
- History of long-standing alcoholism
- Absence of recent gastrointestinal hemorrhage (i.e. <15 days)
- Liver chemistry suggestive of severe AH
- Maddrey function ≥32 (alternative scores such as Glasgow or MELD scores may be used to identify disease severity)
- For patients who will be included in studies evaluating new molecules or therapeutic strategies, transjugular liver biopsy is required

Before starting corticosteroids or pentoxifylline, clinicians need to perform:

- Abdominal ultrasound to exclude other causes of jaundice
- Systematic infectious screenings consisting of chest X-ray, blood, urine and ascites cultures

In patients cured of bacterial infection, corticosteroids may be used

- Screening of hepatitis B, C and HIV virus

The choice between prednisolone and pentoxifylline is based on center practice (criteria to monitor treatment upon therapy are available only for use of corticosteroids)

Management of Alcoholic Hepatitis

40 mg/day of prednisolone for 28 days

Response to therapy may be evaluated after 7 days of therapy using the Lille model

A Lille score ≥0.45 indicating non-response and increased risks of infection and death

In non-responders, the interruption of corticosteroids is recommended particularly in those classified as null responders (Lille score >0.56)

Response to therapy (Lille score <0.45) Corticosteroids may be continued for 28 days

pentoxifylline 400 mg orally 3 times daily

No criteria are available to determine response to therapy

Treatment
Alcoholic Hepatitis

- Abstinence
- Nutritional support
  - Protein, sodium, vitamins, Zn, Mg, Phos
- Propylthiouracil
- Corticosteroids
- Anabolic steroids (oxandrolone)
- Colchicine
- Pentoxifylline
- Liver transplantation
- Emerging therapies: anti TNF ab (?)
Corticosteroids in the treatment of acute alcoholic steatohepatitis

- Anti-inflammatory
- Use of corticosteroids in patients with Maddrey score of >32 if
  - No evidence of gastrointestinal bleeding or infection
  - Evidence of hepatic encephalopathy
- Look for early change in bilirubin levels (Lille criteria):
  - Likely to respond if bilirubin on day 7 is lower than on 1st day of treatment (Mathurin et al 2003).
- Risks:
  - Infection
  - GI bleeding
Effect of corticosteroid therapy on survival in alcoholic hepatitis

- Ramond et al, NEJM 1992, 326:507
Pentoxifylline

- Non-selective phosphodiesterase inhibitor
- Increases intracellular cAMP and cGMP levels
- Inhibits TNFα production
- Used for treatment of claudication (400mg tid)
- Reduces fibroblast proliferation and collagen secretion
- Excellent safety profile
SURVIVAL CURVES FOR THE PTX-TREATED (SOLID LINE) AND CONTROL (DOTTED LINE) GROUPS

PTX (400 mg tid) vs placebo for 4 weeks

Prednisolone With vs Without Pentoxifylline and Survival of Patients With Severe Alcoholic Hepatitis: A Randomized Clinical Trial

Mathurin et al. JAMA Volume 310(10):1033-1041 2013
Prednisolone or Pentoxifylline for Alcoholic Hepatitis

Thursz et al. The New England J of Medicine, vol. 372, no. 17, pp. 1619-1628
Anti-TNF therapy - Clinical studies

- European study (Tilg et al 2003)
  - 12 patients moderate-severe AH
  - treated with Infliximab 5mg/kg single dose iv
  - 10 of 12 patients were alive at 15 month

- US study with TNF receptor antagonist (Menon et al 2004)
  - Open label study with etanercept
  - Showed safety in patients with less severe AH

- Large double-blind randomized study (Tilg et al 2003)
  - Prednisolone or Prednisolone+Infliximab (anti-TNFα antibody)
  - Terminated due to increased infectious complications.
Liver Transplantation in Acute Alcoholic Hepatitis

Kaplan–Meier Estimates of Survival in the 26 Study Patients and the 26 Best-Fit Matched Controls

No. at Risk
Patients undergoing transplantation 26 20 15 14 13
Matched controls 26 6 6 5 4

P<0.001 at 6 mo (primary end point)

P<0.001 at 24 mo (extended follow-up)
Gaps in Knowledge in AH

- Histologic classification
- Clinical definition
- Grading the severity of AH
- Acute, chronic or acute-on-chronic ALD (?)
- Biomarkers
- Organ interactions (gut-liver-brain axis)
- Genetic factors
- Impact of comorbidities
- Other factors affecting patient outcomes
- Effective therapy
Liver inflammation in alcoholic hepatitis is induced and amplified by metabolic danger signals (ATP and uric acid) and gut-derived LPS.

Conclusions:
Endogenous danger signals released from hepatocytes induce a cellular cross-talk and activate the inflammasome in immune cells.
Therapeutic depletion of uric acid ameliorates alcoholic liver disease in mice

Lieber-DeCarli ethanol diet or control diet (pair-feeding) 4 weeks

Depletion of uric acid: allopurinol inhibits synthesis of uric acid

probenecid promotes renal excretion of uric acid + inhibits ATP action

AASLD 2013; Petrasek ..
Szabo
Manuscript under review

Data presented as mean ± SEM (N=9-15 mice/group).
The IL-1 Receptor Binds IL-1β, IL-1 and the IL-1 Receptor Antagonist

Interleukin-1 receptor antagonist (IL-1Ra)
endogenous competitive antagonist

Question:
Could exogenous IL-1 receptor antagonist administration ameliorate ASH?
Administration of IL-1 receptor antagonist attenuates ASH and progression of liver damage in mice
Novel Therapies in Alcoholic Hepatitis

Consortium Administration - UMMS
G Szabo

Clinical Trial
Data collection/Statistics
B Barton

DSMB

Cleveland Clinic
A McCullough

Ut Southwestern
M Mitchell

UMMS
G Szabo

Univ Louisville
C McClain

Translational Project -1
Cleveland Clinic
L Nagy

Translational Project -2
UMMS
G Szabo

Translational Project -3
Univ Louisville
C McClain
Focus on key elements of the pathogenesis of alcoholic hepatitis

- **Inflammatory cascade and innate immune activation**
  - a demarcating feature of 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.
Multicenter randomized double-blind pilot study in severe alcoholic hepatitis

SEVERE AH

MELD 20-31 + DF>32

Prednisone (n = 65)

MELD >31 + DF>32

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

- 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

* IL-1RA: Interleukin-1 Receptor Antagonist
Therapeutic Targets in Alcoholic Liver Disease

**Brain**
- Treat alcohol addiction

**Hepatocyte**
- Caspase inhibitor
- Antioxidants
- PPARα agonist
- SAME

**Stellate cell**
- PPARγ agonist
- Anti-fibrotic agents

**Inflammation**
- Anti-IL-1β/IL-1R blockade
- Inflammasome activation
- Anti MCP-1
- PPAR agonist
- IL-22
- GCSF

**Cell-based therapies**
- Inhibition of activated macrophages

**Mucosal Barrier/inflammation**
- Epithelial tight junctions
  - Zinc
  - FXR agonist
  - miR-155 inhibitor

**Gut**

**Microbiome**
- Probiotics
- Prebiotics
- Non-absorbable antibiotics
- ? Fecal/microbial transplantation

**LPS**

**Macrophage**

- Anti-endotoxin antibodies
- Anti-MCP-1

**Stellate Cell**

**Therapeutic Targets in Alcoholic Liver Disease**
Optimal therapy in alcoholic hepatitis

1. Target key elements of the pathogenesis of alcoholic hepatitis
2. Affordable
3. Oral agent with no side effects

- Metabolic danger signals
- Gut integrity
- Inflammatory cascade and innate immune activation
- Cell survival and death pathways
- Liver regeneration

Consider combination therapy with multiple agents/targets
Thank you
Understanding pathogenesis guides new therapies.

- Hepatocyte damage
- Fatty acids
- Steatosis

Diagram showing the process of liver injury and inflammation:
- Ethanol
- LPS + other PAMPs
- Ethanol
- Fatty acids

Liver inflammation and recruitment of inflammatory cells:
- Kupffer cells
- Monocytes
- T-cells
- NKT cells
- Neutrophils

Chemokines and cytokines:
- MCP-1, MIP-1
- RANTES
- TNFα
- IL-1β
- IL-6
- IL-8

Bone marrow

Mitochondrial damage:
- ROS

Increased bacterial overgrowth and gut permeability: