ABNORMAL LIVER TESTS
Antonio J. Sanchez, M.D.

Transplant Hepatologist
Associate Professor of Medicine
Division of Gastroenterology and Hepatology
University of Iowa Hospitals and Clinics
I, Antonio Sanchez, MD, disclose the following financial relationships with manufacturers of health care products:

Grant/Research Support: Merck, Shire, Ocera, Gilead

I, Antonio Sanchez, MD will not discuss medical devices during my presentation.
OBJECTIVES

Define risk factors of acute and chronic liver disease

Discuss the diagnostic approach of patients with abnormal liver enzymes

Discuss indications for referral to Hepatology
Clinical Scenario

53 y/ Caucasian man

Annual physical exam - Elevated liver enzymes

ALT - 130 (15-30)
AST - 90 (15-30)
Alkaline phosphatase - 105 (60-120)
Total bilirubin - 0.8 mg/dl (0.5 - 1 mg/dl)
Gamma GT - 40 u/L (35-60)
Clinical Scenario

Unaware of liver enzyme elevation
Incidental finding on annual exam
Asymptomatic

PAST MEDICAL HISTORY
Hyperlipidemia

FAMILY HISTORY:
No liver disorders
Clinical Scenario

SOCIAL HISTORY
Lawyer
ETOH: 1-2 beers/week
No smoking, no illicit drugs, no tattoos, no blood transfusions, no herbals or natural products

REVIEW OF SYSTEMS
Fatigue
20-pound weight gain – over past 12 months
No abdominal pain
Clinical Scenario

**PHYSICAL EXAM**
230 pounds – BMI 33
No palmar erythema
Abdomen- Palpable right liver lobe.   No ascites
No stigmata of chronic liver disease on exam

**LABS**
HB 15,  Platelet count is 220,000
Glucose 110 mg/dl
Total cholesterol  250   LDL 150   HDL 30
Tryglicerides – 350
Clinical Scenario

**DIAGNOSTIC APPROACH**

What is the etiology of his liver enzyme elevation?

What is the extent of liver disease?

What are effective management interventions?
LIVER ENZYMES

AST
ALT
ALKALINE PHOPHATASE
GGT
TOTAL BILIRUBIN
5 NUCLEOTIDASE

LIVER ‘FUNCTION TESTS’
PT/INR, SERUM ALBUMIN, FACTOR V
Aminotransferases

Released with hepatocellular injury

Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)

AST/ALT ratio

- Normal is 0.8
- In alcoholic liver disease, is usually > 2
Alkaline Phosphatase

In liver, play an active role in down-regulating the secretory activities of the intrahepatic biliary epithelium

Found in:
- Liver
- Bone
- Intestine
- First trimester placenta
- Kidney

Gamma-glutamyl transpeptidase (GGT):
- Liver origin: Elevated GGT
- Bone origin: Normal GGT
What causes ↑ bilirubin?

- Overproduction by reticuloendothelial system

- Failure of hepatocyte uptake

- Failure to conjugate or excrete

- Obstruction of biliary excretion into intestine
Bilirubin

Used to determine liver’s ability to clear endogenous and exogenous substances from the circulation

- Indirect (unconjugated) bilirubin
  Elevated with hemolysis, hepatic disease

- Direct (conjugated) bilirubin
  Elevated with biliary obstruction and hepatocellular disease.

Jaundice usually develops with a bilirubin $\geq 3$ mg/dL
**Table 1. Causes of Chronically Elevated Aminotransferase Levels.**

<table>
<thead>
<tr>
<th>Hepatic causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol abuse</td>
</tr>
<tr>
<td>Medication</td>
</tr>
<tr>
<td>Chronic hepatitis B and C</td>
</tr>
<tr>
<td>Steatosis and nonalcoholic steatohepatitis</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
</tr>
<tr>
<td>Hemochromatosis</td>
</tr>
<tr>
<td>Wilson’s disease (in patients ≤40 years old)</td>
</tr>
<tr>
<td>Alpha1-antitrypsin deficiency</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nonhepatic causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celiac sprue</td>
</tr>
<tr>
<td>Inherited disorders of muscle metabolism</td>
</tr>
<tr>
<td>Acquired muscle diseases</td>
</tr>
<tr>
<td>Strenuous exercise</td>
</tr>
</tbody>
</table>
Liver Disease and Cirrhosis

- Fatty liver
- Fibrosis
- Hepatitis
- Cirrhosis of the liver
How do we approach a patient with abnormal liver enzymes?
Evaluation & Diagnosis

History!

Sexual contacts

Pregnancy

Medications

Risk Factors

Travel Hx

ETOH use

Metabolic

Illicit drug use
COMPLETE MEDICAL HISTORY

- History and physical exam-

Most important part of the evaluation in a patient with abnormal liver enzymes

- Acute vs. chronic liver disease

- Duration, pattern & progression - enzyme abnormalities

- Recheck liver profile / previous liver profiles
ETOH USE & EXPOSURE TO MEDICATIONS

- Amount /type of ETOH– alcoholic equivalents

- Medications?

(prescription, over-the-counter and herbal therapies)

RX: statins, antibiotics, methotrexate, etc.

OTC’s: acetaminophen/NSAIDS
Acetaminophen toxicity

Acetaminophen toxicity begins with the metabolism of acetaminophen (paracetamol) by cytochrome P450 (CytoP450) enzymes. The activated metabolite N-acetylparabenzoxquinoneimine (NAPQI) binds to cellular proteins, leading to hepatic and renal injury.

- Acetaminophen is metabolized by CytoP450 to form NAPQI.
- NAPQI then reacts with glutathione (GSH) forming an acetaminophen glutathione conjugate.
- The conjugate is excreted in urine.
- A small fraction of acetaminophen is also conjugated to form acetaminophen sulfate.
- UDP-glucuronosyltransferase is involved in the conjugation of acetaminophen to sulfate.

Note: The image indicates that the metabolism pathways are saturated, which can lead to increased toxicity.
Acetaminophen toxicity

Decreased hepatic glutathione stores

ETOH use
Malnutrition
Anorexia nervosa
Bulimia
Cystic fibrosis
Risk factors - Acetaminophen toxicity

Max daily dose –

patients chronic alcohol use: 2 g

- Zimmerman et al: 67 pts with hepatic injury after APAP for therapeutic purposes, all alcoholics
  - 60% < 6 g/day
  - 40% < 4 g/day
  - AST peaks: 3000 to 48,000
  - 20% mortality

RISK FACTORS FOR VIRAL HEPATITIS TRANSMISSION

Illicit substances (IV drug use)

Tattoo placement/Blood Transfusions

Travel History (Endemic areas for hepatitis A - E)

Sexual History (High risk sexual behavior)

Exposure to people with jaundice, contaminated foods
ASSOCIATED MEDICAL PROBLEMS

- Metabolic Disorders (DM, hyperlipidemia, obesity) is a risk factor for non alcoholic fatty liver disease

- Autoimmune disorders (SLE, RA, hypothyroidism)

- CHF/Congestive hepatopathy

- Hx of chronic pancreatitis in alcoholics

- Celiac disease/Inflammatory bowel disease
FAMILY HISTORY

History of liver disorders in family (Hemochromatosis/ AA1AA deficiency)

Viral hepatitis in family (Hepatitis B in Asia)

Autoimmune disorders (hypo thyroidism, Lupus, RA)

History of liver cancer (higher risk in hepatitis B)
PHYSICAL EXAM

Presence/absence - pre-existing liver disease

Stigmata of portal hypertension

Evidence of hepatic decompensation
PHYSICAL EXAM

STIGMATA OF CHRONIC LIVER DISEASE

Spider nevi
Palmar erythema
Gynecomastia
Caput medusae
Dupuytren's contractures
Parotid gland enlargement
Testicular atrophy
Temporal/proximal muscle wasting
Figure 41-5  Systemic clinical manifestations of liver cirrhosis.
LABORATORY TESTING

PATTERNS OF LIVER ENZYME ELEVATION

Hepatocellular

Cholestatic

Mixed
Hepatocellular Injury

Hepatitis A:
- Acute infection
- History: travel, recent outbreak, nausea, vomiting, jaundice
- Labs: Profound ALT/AST. Hepatitis A IgM, elevated bilirubin

Hepatitis B:
- Can be acute or chronic
- History: Patient from Asia, Subsaharan Africa; sexual history, drug use
- Labs: ALT/AST, Hepatitis B surface antigen, Hb core antibody

Hepatitis C:
- History: IV drug abuse, blood transfusion prior to 1992, sexual history, tattoos
- Labs: Hepatitis C antibody (HCV viral load if immunocompromised)
Hepatocellular Injury

Autoimmune Hepatitis

History: Young to middle-aged female
Personal or family history of autoimmune disorders

Labs:
AST/ALT elevation
Anti-nuclear antibody: Positive
Anti-smooth-muscle antibody (SMA)
Serum protein electrophoresis (SPEP) – increase in gamma globulin
Liver biopsy (lymphocytic infiltrate/plasma cells)
Hepatocellular Injury

Non-alcoholic steatohepatitis (NASH)

Increase in AST/ALT are usually less than 4-fold.
Ratio of AST/ALT is usually < 1
History: metabolic syndrome, obesity, diabetes

Labs:
Rule out other causes of liver disease
Abdominal Ultrasound: increased liver echogenicity
Cholestatic Pattern

Medications:
- Anabolic steroids, contraceptives, antibiotics

Total parenteral nutrition (TPN)

Cirrhosis:
- Viral hepatitis (Hepatitis B, C)
- Alcohol hepatitis
Cholestatic Pattern

Primary Biliary Cirrhosis

Autoimmune disease

Predominately in women, usually ages 35-65

History of other autoimmune disorders

Symptoms: Pruritis, fatigue, hyperpigmentation, musculoskeletal complaints

Labs:

- Elevated alkaline phosphatase and GGT
- Anti-mitochondrial antibody
- Liver biopsy to verify diagnosis and/or overlap syndrome
Cholestatic Pattern

Primary Sclerosing Cholangitis

Chronic progressive disorder - inflammation, fibrosis, and stricturing of medium size/large bile ducts in the intrahepatic and extrahepatic biliary tree

~ 90% have inflammatory bowel disease - ulcerative colitis (UC)

Symptoms: Pruritus, fatigue, RUQ pain, UC symptoms

Diagnosis:

- Ultrasound
- ERCP Cholangiogram: multifocal stricturing and dilation of intrahepatic and/or extrahepatic bile ducts

Prognosis:

- 10-15% risk of developing cholangiocarcinoma
- Liver transplant is ultimate only treatment
Cholangiogram
Primary Sclerosing Cholangitis
BACK TO OUR PATIENT
53 y/o man

ALT  130  AST  90  - Normal  Alk phos and T Bili

PLT count, PT/INR is normal

Asymptomatic

No baseline liver enzymes, remain high upon recheck

Hyperlipidemia/weight gain
ADDITIONAL TESTING

Liver enzymes remain elevated, upon recheck

Viral hepatitis serologies for B and C are negative
Iron Studies and Ferritin are normal

LIVER ULTRASOUND: Shows an enlarged liver with diffuse increase echogenicity. No masses, no ductal dilatation or ascites
What is the presumed etiology for his liver enzyme elevation?
NON ALCOHOLIC STEATOHEPATITIS (NASH)
NAFLD - Spectrum of Disease

Steatosis

Steatohepatitis (NASH)

Cirrhosis
Natural History of Fatty Liver (NAFLD)

- Normal Liver
  - Simple Fat
    - Fatty Liver + Scar tissue
  - Fat + Inflammation
    - Cirrhosis
      - Liver Cancer

20%
Epidemiology

Global distribution - Prevalence of NAFLD 13-18%

NAFLD is a leading cause of cryptogenic cirrhosis

Present in all ethnicities, and age groups

NHNAS III  USA 23 % with abnormal liver enzymes

63 % in people with diabetes mellitus
96 % in obese people

Risk Factors for Fatty Liver Disease

- Diabetes
- High TG
- Obesity

Prevalence (%)

### Studies on Non-Alcoholic Steatohepatitis in Asia

<table>
<thead>
<tr>
<th>Country of Origin</th>
<th>N</th>
<th>Advanced hepatic fibrosis</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Australia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western Sydney</td>
<td>66</td>
<td>Cirrhosis 20%</td>
<td>Chitturi</td>
</tr>
<tr>
<td>Brisbane</td>
<td>42</td>
<td>Cirrhosis 6%</td>
<td>Powell</td>
</tr>
<tr>
<td>New Zealand (Auckland)</td>
<td>41</td>
<td>Cirrhosis 2%</td>
<td>Samarsinghe</td>
</tr>
<tr>
<td><strong>North Asia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>China (Hong Kong)</td>
<td>30</td>
<td>Reported Advanced disease</td>
<td>Leung</td>
</tr>
<tr>
<td>Japan</td>
<td>15</td>
<td>Reported Advanced disease</td>
<td>Ueno</td>
</tr>
<tr>
<td><strong>South Asia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>India (New Delhi)</td>
<td>52</td>
<td>Bridging Cirrhosis 12%</td>
<td>Agarwal</td>
</tr>
<tr>
<td>India (Mumbai)</td>
<td>168</td>
<td>Cirrhosis 7%</td>
<td>Amarapurkar</td>
</tr>
<tr>
<td>South Korea (seoul)</td>
<td>39</td>
<td>Reported Advanced disease</td>
<td>Park</td>
</tr>
<tr>
<td>Sri Lanka (Kelaniya)</td>
<td>34</td>
<td>Cirrhosis 10%</td>
<td>Janaki</td>
</tr>
</tbody>
</table>

Source: Asia Pacific Working Party on NASH
NAFLD

Increased overall mortality compared to matched control populations.

Most common cause of death in patients with NAFLD and NASH is cardiovascular disease.

Increased liver-related mortality rate – increasingly common indication for liver transplantation (15-20%).

Fig. 1. Longitudinal trends in the frequency of indications for liver transplantation in the United States are shown for 2002 through 2014. Nonalcoholic steatohepatitis (NASH) and cryptogenic cirrhosis (CC) have been combined to account for the high frequency of NASH as a cause of cryptogenic cirrhosis. Alcoholic liver disease (ALD) has also had a surge as an indication for liver transplantation. HCV, hepatitis C virus. *(Data from Scientific Registry of Transplant Recipients.)*
Diagnosis of NAFLD - Ultrasound

Clinical Predictors

NAFLD FIBROSIS SCORE

Multivariate model: Presence or absence of advanced fibrosis

Age
Hyperglycemia
Body mass index
Platelet count
Albumin
AST/ALT ratio

Independent indicators of advanced liver fibrosis

Diagnosis of NAFLD- Fibroscan

Liver Biopsy

Stage the severity of injury - Exclude other etiologies

Liver biopsy valuable diagnostic test for NASH.

Angulo et al.

Age > 45 years
Obesity
Type 2 diabetes mellitus
AST/ALT ratio >1

Angulo P  Hepatology 30(6):1356–1362, 1999
Differential Diagnosis

Exclude other etiologies of elevated liver enzymes

Viral

Autoimmune

Metabolic

Genetic
Steatosis - Macrovacuolae
Steatosis + lobular inflammation
Fibrosis Extension
Cirrhosis
NASH - How to Treat?

First Hit

- Insulin resistance
- $\uparrow$ Fatty acids

Second Hit

- Steatosis
- Lipid peroxidation

Treatment Options:

- Insulin Sensitizers
- Antihyperlipidemic
- Antioxidants
- Cytoprotectants
- Weight Loss
- Diet/Exercise

How to Treat?
Weight Loss

Explain diagnosis and set realistic target weight
Nutritional counseling – refer to dietician
Exercise – 3-4 times per week, expend 400 kcal per session

Promrat et al 2010: Intensive lifestyle intervention (diet, exercise, behavior modification) vs structured education alone.

- **Weight loss 9.3% vs 0.2% (p = 0.003)**
- **Decrease in NAS 72% vs 30% (p=0.03)**

Fibrosis (45%)

NASH Resolution (64%–90%)^a

Ballooning/Inflammation (41%–100%)^a

Steatosis (35%–100%)^a

Weight Loss ≥10%^12

Weight Loss ≥7%^12

Weight Loss ≥5%^5,7,12

Weight Loss ≥3%^5,7,12-13
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Type of Surgery</th>
<th>Mean Age</th>
<th>Mean BMI</th>
<th>Mean Follow-Up Interval</th>
<th>% Change in Weight/BMI</th>
<th>Steatosis Improvement</th>
<th>Pericellular Fibrosis Change</th>
<th>Hepaticellular Injury Improvement</th>
<th>NASH Resolution</th>
<th>Histopathologic Worsening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dixon et al</td>
<td>2004</td>
<td>36</td>
<td>LAGB</td>
<td>43 (10.3)</td>
<td>47 (10.6)</td>
<td>25.6 mo</td>
<td>34 kg</td>
<td>52%</td>
<td>Significant (p &lt; 0.001)</td>
<td>91% improvement; 70% complete resolution</td>
<td>100%</td>
<td>82%</td>
</tr>
<tr>
<td>de Almeida et al</td>
<td>2006</td>
<td>16</td>
<td>RYGBP</td>
<td>40.2 (9.5)</td>
<td>53.4 (8.8)</td>
<td>23.5 mo</td>
<td>22.3 kg</td>
<td>42%</td>
<td>75% complete resolution</td>
<td>50% improvement</td>
<td>69% complete resolution</td>
<td>94%</td>
</tr>
<tr>
<td>Barker et al</td>
<td>2006</td>
<td>19</td>
<td>RYGBP</td>
<td>48.6</td>
<td>47 (4.4)</td>
<td>21.4 mo</td>
<td>18 kg</td>
<td>52.4%</td>
<td>100%</td>
<td>47% improvement</td>
<td>89%</td>
<td>10.5% had mild fibrosis increase</td>
</tr>
<tr>
<td>Mattar et al</td>
<td>2005</td>
<td>70</td>
<td>RYGBP (41)</td>
<td>49 (9)</td>
<td>56 (11)</td>
<td>15 mo</td>
<td>48.8 kg</td>
<td>59%</td>
<td>37% complete resolution</td>
<td>NA</td>
<td>75%</td>
<td>None</td>
</tr>
<tr>
<td>Mathurin et al</td>
<td>2006</td>
<td>185 (121)</td>
<td>LSG (23)</td>
<td>BIB, LAGB</td>
<td>40.6</td>
<td>47.1</td>
<td>12 mo</td>
<td>27 kg</td>
<td>19%</td>
<td>Significant (p &lt; 0.0001)</td>
<td>0.14 to 0.38 (p = 0.38)</td>
<td>NA</td>
</tr>
<tr>
<td>Mottin et al</td>
<td>2005</td>
<td>90</td>
<td>RYGBP (majority)</td>
<td>35.6 (1.1)</td>
<td>46.7 (0.88)</td>
<td>12 mo</td>
<td>NA</td>
<td>81.4%</td>
<td>82.2% (54% complete resolution)</td>
<td>NA</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>Clark et al</td>
<td>2005</td>
<td>16</td>
<td>RYGBP</td>
<td>43.9 (8.1)</td>
<td>51.1 (6.1)</td>
<td>305 d</td>
<td>53.7 kg</td>
<td>35.4%</td>
<td>81% complete resolution</td>
<td>43%</td>
<td>86%</td>
<td>81%</td>
</tr>
<tr>
<td>Furuya et al</td>
<td>2007</td>
<td>18</td>
<td>RYGBP</td>
<td>46.8 (7.3)</td>
<td>51.7 (7.4)</td>
<td>24 mo</td>
<td>19.3 kg</td>
<td>38%</td>
<td>89% (84% complete resolution)</td>
<td>75% of cases resolved fibrosis</td>
<td>50%</td>
<td>No patients with NAS of &gt; 4</td>
</tr>
<tr>
<td>Liu X et al</td>
<td>2007</td>
<td>39</td>
<td>RYGBP</td>
<td>41.4 (9)</td>
<td>47.7 (6.2)</td>
<td>18 mo</td>
<td>50.2 kg</td>
<td>38.2% BMI</td>
<td>97% resolved macrosteatosis</td>
<td>Centrilobular fibrosis improvement: 50% → 25%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Kral et al</td>
<td>2004</td>
<td>104</td>
<td>BPD</td>
<td>36.9 (9)</td>
<td>47 (8.4)</td>
<td>41 mo</td>
<td>38 kg</td>
<td>34%</td>
<td>Decreased from grade 1.57 to 0.52 (p &lt; 0.0001)</td>
<td>Severe fibrosis improvement in 27% of patients; 40% developed mild fibrosis</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Csendes et al</td>
<td>2006</td>
<td>16</td>
<td>RYGBP</td>
<td>46.2</td>
<td>44.3</td>
<td>17.5 mo</td>
<td>15.7 kg</td>
<td>35%</td>
<td>93%</td>
<td>4/5 (80%)</td>
<td>5/5 (100%)</td>
<td>100% (5 pts)</td>
</tr>
</tbody>
</table>

BIB, biliointestinal bypass; BPD, biliary pancreatic diversion; BMI, body mass index; LAGB, laparoscopic adjustable band; LSG, laparoscopic sleeve gastrectomy; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; RYGBP, Roux-en-Y gastric bypass.
Antioxidants

Vitamin E

Sanyal et al. NEJM 2010

247 adults – NASH, non diabetic

Pioglitazone
Vitamin E
Placebo

For 96 weeks

Primary outcome - improvement in liver histology
Antioxidants

Vitamin E

Sanyal et al. NEJM 2010

Vitamin E vs. Placebo improvement in NASH 43 % vs. 19 %

Pioglitazone vs. Placebo not significant (34% and 19%)

Vitamin E and Pioglitazone reduced aminotransferases
reduced hepatic steatosis

No improvement in fibrosis scores

Pioglitazone group gained more weight
Farsenoid Nuclear Receptor Activators

Obeticholic Acid


141 patients with NASH
142 patients with NASH

Obeticholic acid
Placebo

45% in Obeticholic acid group improved liver histology
21% in placebo group improved liver histology
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Primary Proposed Mechanism of Action</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>FXR agonist</td>
<td>Carbohydrate, lipid metabolism, and regulation of insulin sensitivity</td>
<td>OCA</td>
</tr>
<tr>
<td>Insulin sensitizers</td>
<td>PPAR alpha/delta agonists</td>
<td>Elafibranor (GFT505)</td>
</tr>
<tr>
<td></td>
<td>SGLT2 Inhibitors</td>
<td>Remogliflozin etabonate</td>
</tr>
<tr>
<td></td>
<td>GLP-1 receptor agonists</td>
<td>Liraglutide (GLP-1 analogue)</td>
</tr>
<tr>
<td></td>
<td>Angiotensin-converting enzyme inhibitors and angiotensin-II receptor</td>
<td>Telmisartan, losartan</td>
</tr>
<tr>
<td></td>
<td>blockers</td>
<td></td>
</tr>
<tr>
<td>Modulators of lipogenesis</td>
<td>n-3 PUFAs</td>
<td>Ethyl-eicosapentanoic acid (EPA-E)</td>
</tr>
<tr>
<td></td>
<td>Fatty acid–bile acid conjugates</td>
<td>Aramchol</td>
</tr>
<tr>
<td></td>
<td>LXR-α inhibitor</td>
<td>Oltipraz</td>
</tr>
<tr>
<td>Antioxidants</td>
<td>GSH repletion</td>
<td>Cysteamine</td>
</tr>
<tr>
<td>Antiinflammatory/apoptotic</td>
<td>Caspase inhibitor</td>
<td>Emriscan and GS-9450</td>
</tr>
<tr>
<td></td>
<td>Chemokine receptor type 2 and 5 antagonants</td>
<td>Cenicriviroc</td>
</tr>
<tr>
<td>Antifibrotic agents</td>
<td>Monoclonal antibody (IgG4) against LOXL2</td>
<td>Simtuzumab</td>
</tr>
<tr>
<td></td>
<td>Galectin-3 inhibitor</td>
<td>GR-MD-02</td>
</tr>
</tbody>
</table>
Key NASH Therapies: Improvement in Fibrosis

- Results from separate studies, not head to head
  - Time points and populations may differ among studies

- Cenicriviroc 150 mg/day
- Obeticholic Acid 25 mg/day
- Elafibranor 120 mg/day
- Vitamin E 800 IU/day
- Pioglitazone 30 mg/day

* No data

- Selonsertib 6 or 18 mg/day

P-values:
- Vitamin E 800 IU/day: \( P = .24 \)
- Pioglitazone 30 mg/day: \( P = .12 \)
- Obeticholic Acid 25 mg/day: \( P = .004 \)
- Elafibranor 120 mg/day: \( P = .02 \)
- Selonsertib 6 or 18 mg/day: \( P = \text{NS} \)
Clinical Trials in Hepatology

Phase II Double-blind, Randomized, Placebo-controlled, Dose-finding Study to Evaluate the Safety, Tolerability and Efficacy of Volixibat Potassium, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi) in Adults With Nonalcoholic Steatohepatitis (NASH)

Volixibat increases bile acid excretion

Regulation
- Hepatic bile acid concentrations
- Fatty acid metabolism in the liver

Potential anti-fibrotic effect
Referral to Hepatology

Persistent elevation of aminotransferases

Work up is abnormal

Evidence of portal hypertension

Decision for liver biopsy/perform Fibroscan

Access to clinical trials
Summary

Recheck liver profile/ previous labs for progression

Complete history and physical exam

Define patient risk factors for liver disease

Behavior modification/changes
Summary

Fatty liver disease is the hallmark of insulin resistance and reflects the metabolic syndrome affecting the liver.

NASH is a progressive liver disease, associated with a risk of developing cirrhosis and hepatocellular carcinoma.

Liver elastography is a reliable non-invasive method for the diagnosis of NAFLD.
No FDA approved pharmacologic interventions for NASH - Clinical Trials

Dietary changes associated with gradual weight loss lead to biochemical/histologic improvement in NASH

Early identification of patients at risk for NAFLD essential to prevent complications
Transplants save lives