Evaluation of Abnormal Liver Function Tests

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Disclosure Information

(Relevant Speaker Financial Relationships)

- Dr David Leff discloses the following relevant financial relationships with commercial interests within the past twelve months:
  - Gilead, Abbvie: Speakers’ Bureau
LEARNING OBJECTIVES

1. Understand the different laboratory and radiographic markers for liver disease
2. Recognize the differential diagnosis and subsequent work up
3. Gain an understanding of the major liver diseases we face and their treatments

“Liver Function Tests”

LFT’s Do Not measure “function”

AST/ALT = “activity”
Albumin/PT/Cholesterol/Glucose = “function”
Bilirubin = hepatic transport capability
Alk Phos = bile duct injury
ALT and AST

- Enzymes, found in Hepatocytes
  Released when liver cells damaged
- ALT is specific for liver injury
- AST (SGOT) is also found in skeletal and cardiac muscle

PROTHROMBIN TIME/INR

- Measure of the Vitamin K dependent clotting factors ie. II, VII, IX and X.
- The liver is involved in activating Vitamin K. With liver damage, these clotting factors cannot be produced.
- Make sure the patient has adequate Vitamin K by giving 10mg sc.
- Giving Vitamin K has no effect on INR if patient has impaired synthetic function.
ALBUMIN

- Albumin has a half life of 21 days, so the drop that occurs with hepatic dysfunction does not occur acutely
- But an acute illness can cause albumin to drop rapidly due to cytokines increasing the rate of albumin metabolism
- HOWEVER, don’t forget that low albumin also occurs in NEPHROTIC syndrome, so always check the urine for protein.

"Abnormal LFTs"

Study of 249 donors with abnormal LFTs

30% ETOH liver disease
40% Fatty liver
18% Hep C
6% Miscellaneous
5% No diagnosis

“Abnormal LFTs”

81 of 1124 patients with abnormal LFTs

Negative serologic work-up

Biopsied:

- NASH/fatty liver 84%
- No diagnosis 10%
- Cirrhosis/fibrosis 6%

Daniel, S. Am J Gastro 1999

TYPICAL PATTERNS

- HEPATOCELLULAR
  - Increased transaminases
    - Viral Hepatitis
    - Drugs/alcohol
    - Autoimmune
    - NASH
    - Hemochromatosis

- CHOLESTATIC
  - Increased Alk Phos and Bilirubin
  - Also may cause increased transaminases
    - Gallstones
    - Primary Biliary Cirrhosis
    - Sclerosing Cholangitis
    - Pancreatic C/a
History

- Viral risk factors/exposure
- Medications/drug/alcohol history
- Travel/work history
- Fevers/weight loss/abdominal pain
- Rash/jaundice/arthlagia/myalgia/kidney disease/pruritis
- Onset/time frame of LFT
- Male/Female

Exam

- Rash/bruising/jaundice
- Ascites/edema
- Encephalopathy
- Temporal/proximal muscle wasting
- Palmar erythema, Spider nevi, Caput Gynecomastia
Exam (cont)

- Dupuytren’s contractures
- Parotid gland enlargement
- Testicular atrophy
- Right pleural effusion
- Liver/spleen size
- Umbilical hernia

What is the sign...and who was it named for?
Medusa

Hepatitis panel, Viral studies
Iron, TIBC, Ferritin
ANA, ASMA, Anti LKM, SPEP
AMA
Triglyceride, Hgb A1C
Ceruloplasmin, Alpha-1-Antitripsin
ProTime/INR
Imaging/Invasive testing

- Ultrasound
- CT
- MRI/MRCP
- ERCP
- Liver biopsy
- Endoscopic Ultrasound
- Elastography/Fibroscan

Evaluation of Elevated LFTs

**Predominantly hepatocellular**

- Viral hepatitis
- Fatty Liver
- Hemochromatosis
- Toxic hepatitis (drugs, herbs, ETOH)
- Autoimmune hepatitis (young women)
- Wilson’s (young adults)/Alpha-1-AT
Drug/ Toxin Induced Hepatitis

Thorough history/timing

Labs: AST/ALT 100-3000
    Bilirubin nl-marked elevation
    Eosinophilia

Environmental toxins

vinyl chloride, herbal preparations with pyrrolizidine alkaloids (Jamaica bush tea), Amanita phalloides mushrooms

Drugs implicated in idiosyncratic liver injury

<table>
<thead>
<tr>
<th>Infrequent But Not Rare</th>
<th>Rare</th>
<th>Combination Agents with Enhanced Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Didanosine</td>
<td>Ethanol-acetaminophen</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Sustiva</td>
<td>Trimethoprim-sulfamethoxazole</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Metformin</td>
<td>Rifampin-isoniazid</td>
</tr>
<tr>
<td>&quot;Statins&quot;</td>
<td>Ofloxacin</td>
<td></td>
</tr>
<tr>
<td>Propylthiouracil</td>
<td>Ketoconazole</td>
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</tr>
<tr>
<td>Halothane</td>
<td>Methyldopa</td>
<td></td>
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<tr>
<td>Disulfiram</td>
<td>Allopurinol</td>
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<tr>
<td>Valproate</td>
<td>Nefazodone</td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Quetiapine</td>
<td></td>
</tr>
<tr>
<td>Dapsone</td>
<td>Isosulfurane</td>
<td></td>
</tr>
<tr>
<td>Herbals</td>
<td>Lisinopril</td>
<td></td>
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<tr>
<td></td>
<td>Nicotinic acid</td>
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<tr>
<td></td>
<td>Imipramine</td>
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<td></td>
<td>Gemtuzumab</td>
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<td></td>
<td>Ecstasy</td>
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<tr>
<td></td>
<td>Labetalol</td>
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<tr>
<td></td>
<td>Flutamide</td>
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</tr>
</tbody>
</table>
ETOH Hepatitis

AST 2x ALT
Elevated GGTP
Large liver
Look for signs of advanced liver disease
Treatment: stop alcohol and steroids if severe acute inflammation, supportive care

Natural history of alcoholic liver disease

- Normal liver
  - 90% - 100%

- Steatosis
  - 10% - 35%
  - 8% - 20%
  - ?

- Alcoholic hepatitis
  - 40% - 50%

- Fibrosis

- Cirrhosis

Alcohol intake
Abstinence effect
?Abstinence effect
### Acute Viral Hepatitis

<table>
<thead>
<tr>
<th>Test</th>
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</thead>
<tbody>
<tr>
<td>Hepatitis A IgM</td>
</tr>
<tr>
<td>Hepatitis B Surface Ag</td>
</tr>
<tr>
<td>Hepatitis B Core IgM Ab</td>
</tr>
<tr>
<td>Hepatitis C PCR</td>
</tr>
<tr>
<td>CMV IgM</td>
</tr>
<tr>
<td>EBV panel, HSV IgM</td>
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</tbody>
</table>

### Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
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</thead>
<tbody>
<tr>
<td>Fever (60%–80%)</td>
</tr>
<tr>
<td>&quot;Flu&quot;-like features (&gt;70%)</td>
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<tr>
<td>Nasal congestion</td>
</tr>
<tr>
<td>Sore throat</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Chills</td>
</tr>
<tr>
<td>Myalgia</td>
</tr>
<tr>
<td>Abdominal discomfort or pain (60%–70%)</td>
</tr>
<tr>
<td>Dark or brown urine (75%–85%)</td>
</tr>
<tr>
<td>Other signs</td>
</tr>
<tr>
<td>Macular erythema</td>
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<tr>
<td>Irritability</td>
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<tr>
<td>Decreased gustatory acuity</td>
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<tr>
<td>Jaundice (20%–30%)</td>
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<tr>
<td>Fatigue, weakness (75%–90%)</td>
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<td>Pruritus (25%–45%)</td>
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<tr>
<td>Anorexia and weight loss (80%–90%)</td>
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<tr>
<td>Diarrhea/constipation (25%)</td>
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<tr>
<td>Nausea, emesis (52%–90%)</td>
</tr>
<tr>
<td>Light- or clay-colored stools (20%–60%)</td>
</tr>
</tbody>
</table>
Viral Hepatitis Therapy

- Follow synthetic functioning
- Supportive care
- Prophylaxis of contacts
- Follow viral studies

CHRONIC VIRAL HEPATITIS

- Exposure history

Hepatitis B: Surface Ag/Ab, Core Ab, E Ag, DNA positive
Hepatitis C: Ab and PCR RNA positive
Hepatitis B virus worldwide

Chronic HBV in the United States Prevalence in Urban Asian Americans

- Community screening of 1836 foreign-born Asians in NYC
- Overall HBV prevalence was 23.8%
  - Prior estimates were 10-15% in similar populations
- Higher prevalence associated with:
  - Chinese vs Other Asian Countries (32.9% vs. 11.3%)
  - Family history (42.5% vs. 18.1%)
  - Male (30.9% vs. 15.4%)
  - Age 19-40 yo (33.8% vs 17.2%)
- No immunity detected in 27.6% -> referred for vaccination
- Only 48.6% showed evidence of previous vaccination

Interpretation of serologic tests for hepatitis B virus infection

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>Total Anti-HBc</th>
<th>IgM Anti-HBc</th>
<th>Anti-HBs</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
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</tbody>
</table>

- Susceptible, never infected
- Acute infection, early incubation
- Acute infection
- Acute resolving infection
- Past infection, recovered, and immune
- Chronic infection
- False positive (ie, susceptible), past infection, or "low-level" chronic infection
- Immune if titer is ≥ 10 m IU/mL

*Transient HBsAg positivity (lasting ≤ 18 d) might be detected in some patients during vaccination.*
Chronic Hepatitis B Goals of Treatment

• Long-term outcomes:
  – Sustained suppression of HBV replication
  – Prevention of ESLD, HCC, transplant, and death
  – Similar goals for both HBeAg+ and HBeAg-

• Therapeutic goals:
  – Undetectable serum HBV DNA
  – Normalization of serum ALT level
  – Loss of HBsAg
  – Improvement in liver histology

US Treatment Algorithm - Resistance Profile: First-Line Treatment Options Have the Lowest Resistance Rates

Resistance does not appear to emerge during treatment with IFN α-2b or PegIFN α-2a

AASLD HCC Surveillance Recommendations

- Surveillance for HCC should be performed using ultrasonography
- Patients should be screened at 6 month intervals
- The surveillance interval does not need to be shortened for patients at higher risk for HCC


Hepatitis C

3,500,000 Infected
1,750,000 Diagnosed
315,000 Cured

*HCV detected-positive HCV RNA and HCV antibody tests.
*Sustained virologic response (SVR).
Symptoms and signs

Extrahepatic manifestations of hepatitis C

Arthralgias
Purpura
Raynaud's phenomenon
Peripheral neuropathy
Essential mixed cryoglobulinemia
B-cell non-Hodgkin's lymphoma
Porphyria cutanea tarda
Membranoproliferative glomerulonephritis
Lichen planus
Sjögren's syndrome
Diabetes mellitus type 2

Vasculitis and cryoglobulinemia related to hepatitis C virus
Porphyria cutanea tarda

While Estimated Prevalence of Chronic HCV Peaked in 2001, Cirrhosis Will Peak Around 2020

- Cirrhosis accounted for just 5% of all cases (diagnosed and undiagnosed) of chronic HCV in 1989, but 10% in 1998 and 20% in 2006.
- Chronic HCV cirrhosis and its complications will continue to rise during the next decade (24.8% of cases projected by 2010 and 37.2% in 2020), reaching its highest prevalence about 40 years after the peak of acute infections and primarily affecting those >60 years of age.

HCV: hepatitis C virus.
HCV Can Start With You

**SCREEN** for HCV Antibodies
- A simple blood test will reveal if your patient has been exposed to HCV

**DIAGNOSE** with an HCV RNA Test
- If the screening test is positive, the RNA test can detect the presence of HCV RNA to confirm a chronic infection

**CONNECT** to an HCV Specialist
- Refer all chronically infected patients to an HCV specialist for treatment evaluation, regardless of presence of symptoms or disease severity

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Current Screening Guidelines

- Screening based on risk factors alone was not optimal
  - Many patients have no known exposure risk
  - Baby boomers (born between 1945 and 1965) account for 75% of all HCV patients
- The CDC, USPSTF, and AASLD issued updated guidelines to include the one-time screening of all baby boomers
- This age cohort should be screened regardless of symptoms or other risk factors
- Along with baby boomers, other high-risk groups to screen include people who currently inject or ever injected drugs, those who received a tattoo in an unregulated setting, and those who had a blood transfusion before 1992

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EPCLUSA Delivered High Cure With a Single-tablet Regimen for All Genotypes

98% OF GT 1-6 SUBJECTS OVERALL ACHIEVED A CURE
Across ASTRAL-1, ASTRAL-2, and ASTRAL-3 EPCLUSA Phase 3 Studies
(n=1015/1035)

GT 1-6 patients without cirrhosis or with compensated cirrhosis take
12 weeks of RBV-free EPCLUSA once daily

*These studies did not include patients with decompensated cirrhosis (Child-Pugh B or C).

Hereditary Hemochromatosis

Most common autosomal recessive genetic disorder

75% are asymptomatic
HFE Mutations (C282Y, H63D)
Prevalance 5:1000 Caucasions
>1 million Americans
# Hereditary Hemochromatosis

![Diagram of symptoms with hereditary hemochromatosis]

## Symptoms with hereditary hemochromatosis

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Occurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness, lethargy, fatigue</td>
<td>40-85</td>
</tr>
<tr>
<td>Apathy, lack of interest</td>
<td>40-85</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>30-60</td>
</tr>
<tr>
<td>Weight loss</td>
<td>30-60</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>40-60</td>
</tr>
<tr>
<td>Loss of libido, impotence</td>
<td>30-60</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>20-60</td>
</tr>
<tr>
<td>Congestive heart failure symptoms</td>
<td>0-40</td>
</tr>
</tbody>
</table>
Hemochromatosis Labs

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Hemochromatosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron, μg/dL</td>
<td>50-150</td>
<td>180-300</td>
</tr>
<tr>
<td>Transferrin, mg/dL</td>
<td>250-370</td>
<td>200-300</td>
</tr>
<tr>
<td>Transferrin saturation, &amp;perc;</td>
<td>20-30</td>
<td>80-100</td>
</tr>
<tr>
<td>Ferritin, ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>20-300</td>
<td>500-6000</td>
</tr>
<tr>
<td>Women</td>
<td>15-250</td>
<td>500-6000</td>
</tr>
<tr>
<td>Genetic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotyping for HFE mutations</td>
<td></td>
<td>C282Y/C282Y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C282Y/H63D</td>
</tr>
</tbody>
</table>

Fatty Liver/ Non-Alcoholic Steatohepatitis

AST/ALT < 4x normal with 1:1 ratio
Female>Male
Obesity
Diabetes
Hypertriglyceridemia
Metabolic syndrome
Natural History of NAFLD

- **Isolated Fatty Liver**
  - None to very minimal progression to fibrosis
  - No ↑ risk of death compared with the general population

- **Fatty Liver with Mild Inflammation**
  - Possible sampling variability with some risk of progression

- **NASH**
  - ~11% over 15 years, but significant
  - ↑ risk of death compared with general population
  - Cardiovascular, malignancy, liver-related
  - NASH with fibrosis portends worse prognosis
    - Fibrosis progression associated with diabetes, severe IR, weight gain >5 kg, rising ALT, AST

- **NASH Cirrhosis**
  - ~31% over 8 years
  - Possible sampling variability with some risk of progression

- **HCC**
  - ~7% over 6.5 years

- **Decompensation**


Global Epidemiology of NAFLD

- 20% Global Epidemiology of NAFLD
- **NAFLD Prevalence (%)**
  - **Overall**: 25.24
  - **Africa**: 13.48
  - **Europe**: 23.71
  - **N. America**: 24.13
  - **Asia**: 27.37
  - **S. America**: 30.45

Systematic literature search
- 729 studies evaluated, 86 studies included
- 57 studies analysed NAFLD prevalence, 15 studies analysed for NASH prevalence

Abbreviations: N, North; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; S, South.
Risk Stratification in NASH

Clinical
- Older age
- Male gender
- Metabolic syndrome
- Diabetes mellitus (DM)
- Family history of DM
- AST/ALT ratio
- Low platelets
- PNPLA3 genotype

Histologic
- Advanced fibrosis
- Fibrosis
- Portal inflammation
- NASH
- Ballooning

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; NASH, nonalcoholic steatohepatitis.

NAFLD and Liver Transplantation

Annual trends in new liver transplant waitlist registrations

Fatty Liver/ NASH

Initial radiologic evaluation
- Ultrasound
- CT
- MR Elastography
- Elastography
- Biopsy

Transient Elastography

- FibroScan® is based on patented technology: Vibration Controlled Transient Elastography (VCTE™)
- Allows painless and simultaneous measurement of two quantitative parameters:
  - Liver stiffness expressed in kPa
    - Correlated to liver fibrosis [1]
  - Controlled Attenuation Parameter (CAP™) expressed in dB/meter
    - Correlated to liver steatosis [2]
- Both quantitative parameters are assessed on the same volume of liver tissue (3cm³)
  - 100 times bigger than liver biopsy
Fibrosis (45%)
NASH Resolution (64-90%)*
Ballooning/Inflammation (41-100%)*
Steatosis (35-100%)*

Weight Loss Pyramid

Weight Loss ≥ 10%¹
Weight Loss ≥ 7%¹
Weight Loss ≥ 5%¹,²,³
Weight Loss ≥ 3%¹,²,³,⁴

*Depending on degree of weight loss
Weight Loss Correlates to Frequency of Clinic Visits

Relative amount of time spent with health care provider discussing weight loss and lifestyle change in 1 year (assuming 4 visits of 15 minutes each)

1/100 of 1 percent

Minutes in 1 year = 525,960

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Exercise

- NAFLD patients engage in less physical activity
  - Fewer than 20% meet recommended physical activity guidelines
- Study by Kistler, et al:
  - 813 adults with NAFLD
    - 54% of patients reported NO physical activity
- NAFLD patients meeting vigorous exercise recommendations (≥ 6 mets for 75 min/wk) assoc with decreased adjusted odds of having NASH (OR 0.65, 95% CI 0.43-0.98, p=0.04)
Exercise: METs

<table>
<thead>
<tr>
<th>Physical activity</th>
<th>MET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light intensity activities</td>
<td></td>
</tr>
<tr>
<td>sleeping</td>
<td>0.9</td>
</tr>
<tr>
<td>watching/television</td>
<td>1.0</td>
</tr>
<tr>
<td>writing, desk work, typing</td>
<td>1.8</td>
</tr>
<tr>
<td>walking, 1.7 mph (2.7 km/h), level ground, striding, very slow</td>
<td>2.3</td>
</tr>
<tr>
<td>walking, 2.5 mph (4 km/h)</td>
<td>2.9</td>
</tr>
<tr>
<td>Moderate intensity activities</td>
<td>3 to 6</td>
</tr>
<tr>
<td>bicycling, stationary, 56 watts, very light effort</td>
<td>3.0</td>
</tr>
<tr>
<td>walking 3.0 mph (4.8 km/h)</td>
<td>3.3</td>
</tr>
<tr>
<td>calisthenics, home exercise, light or moderate effort, general</td>
<td>3.5</td>
</tr>
<tr>
<td>walking 3.4 mph (5.5 km/h)</td>
<td>3.6</td>
</tr>
<tr>
<td>bicycling, &lt;10 mph (16 km/h), leisure, to work or for pleasure</td>
<td>4.0</td>
</tr>
<tr>
<td>bicycling, stationary, 100 watts, light effort</td>
<td>5.5</td>
</tr>
<tr>
<td>Vigorous intensity activities</td>
<td>&gt; 6</td>
</tr>
<tr>
<td>jogging, general</td>
<td>7.0</td>
</tr>
<tr>
<td>calisthenics (e.g., pushups, situps, pull-ups, jumping jacks), heavy, vigorous effort</td>
<td>8.0</td>
</tr>
<tr>
<td>running, jogging, in place</td>
<td>10.0</td>
</tr>
</tbody>
</table>

Obeticholic Acid: FXR Agonist and Bile Acid Analogue

CDCA (chenodeoxycholic acid) ↔ OCA (6-ECDCA) (obeticholic acid)

- ~ 90 x increased potency

- FXR EC50 = 8.7 µM ↔ FXR EC50 = 99 nM

- In vitro/in vivo studies do not necessarily correlate with clinical response

**FLINT: Obeticholic Acid in Noncirrhotic Pts With NASH**

- Double-blind, placebo-controlled, randomized, multicenter phase IIb trial

**Pts with NASH or borderline NASH confirmed by entry biopsy, NAS ≥ 4 (individual scores each ≥ 1), no cirrhosis (N = 283)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Wk 72 Improvement in NAS ≥ 2 Points With No Worsening of Fibrosis</th>
<th>Wk 72 Improvement in Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obeticholic acid 25 mg PO QD (n = 141)</td>
<td>45% (50/110)</td>
<td>35% (36/102)</td>
</tr>
<tr>
<td>Placebo (n = 142)</td>
<td>21% (23/109)</td>
<td>19% (19/98)</td>
</tr>
</tbody>
</table>

\( P = .0002 \) \( P = .004 \)


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**Dual PPARa/d Agonist**

- **Elafibranor**
  - **PPARa**
    - Fatty acid oxidation
    - TG lowering
    - HDL raising
    - Inflammation
  - **PPARd**
    - Lipoprotein metabolism
    - Glucose homeostasis
    - Energy metabolism
    - Inflammation

Liver

Slide courtesy of Bart Staels, MD.
GOLDEN-505: Elafibranor for 52 Wks

- Double-blind, placebo-controlled, randomized, international phase IIb trial

<table>
<thead>
<tr>
<th>Wk 52</th>
<th>Protocol-Defined Primary Outcome*</th>
<th>Modified Definition of Response†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elafibranor 80 mg PO QD (n = 93)</td>
<td>23% (21/93)</td>
<td>13% (12/93)</td>
</tr>
<tr>
<td>Elafibranor 120 mg PO QD (n = 91)</td>
<td>21% (19/89)</td>
<td>19% (17/89)</td>
</tr>
<tr>
<td>Placebo (n = 92)</td>
<td>17% (16/92)</td>
<td>12% (11/92)</td>
</tr>
</tbody>
</table>

*Disappearance of steatosis, ballooning, or lobular inflammation.†Disappearance of ballooning and disappearance or mild persistence of lobular inflammation.


Non-hepatic causes for LFTs

- Muscle injury (initially AST>ALT) polymyositis/seizures/exercise/long distance running Creat kinase, LDH, aldolase
- Thyroid disorders unclear mechanism
- Celiac disease
  - AST/ALT 2x normal return to normal with gluten free diet
- Adrenal insufficiency (Addison’s)
  - AST/ALT 2x normal
Three “Autoimmune” liver diseases

- They are easily confused:
  - Autoimmune hepatitis
  - Primary Biliary Cirrhosis/Cholangitis
  - Primary Sclerosing Cholangitis

Autoimmune Hepatitis

- Cell mediated immune attack against hepatocyte
- Inherited and triggered by environmental factors
- Circulating autoantibodies (ANA, smooth muscle, anti-LKM, anti-SLA)
- Arthralgias, rash, sicca syndrome
- Young women
Autoimmune Hepatitis

ALT/AST 100-1000
Hypergammaglobulinemia
Treat with steroids and Imuran for 1-2 years
6 month mortality of 40%
50% relapse after therapy

Primary Biliary Cirrhosis

- Consider in any patient with autoimmune disease presenting with liver disease (Thyroid, RA, Sjogrens, Systemic Sclerosis)
- Increased Alk phos and Antimitochondrial/AMA positive
- Damage to intralobular bile ducts by chronic granulomatous inflammation
- Unable to excrete bile, therefore present with malabsorption of fat soluble vitamins.
- Present with lethargy, itching and increased Alk Phos in a middle-aged woman.
- May have hyperlipidemia
Primary Sclerosing Cholangitis

- Seen in patients with UC and HIV
- Inflammation, fibrosis and strictures of biliary tree causing “Beaded biliary tree” on ERCP
- Chronic biliary obstruction leads to cirrhosis
- Presentation: Asymptomatic, high Alk Phos, Jaundice, pruritus, abd pain and fatigue
- Dx: High bilirubin and Alk phos but NEGATIVE AMA/ANA
- Mgt: Steroids, Cholestyramine or ursodeoxycholic acid to treat the pruritis and cholestasis but does not affect disease process
- Liver transplant for endstage disease but 20% recur.

Wilson Disease

- Under age 40
- Chromosome 13
- Copper transport protein
- Decreased hepatic excretion of copper into bile
Clinical manifestations of Wilson disease

Neuropsychiatric disorders
Kayser-Fleischer rings
Cardiomyopathy
Liver disease
Steatosis
Chronic hepatitis
Cirrhosis
Fulminant hepatic failure
Hemolysis
Osteopenia
Renal disease
Fanconi's syndrome

Neurologic presentation of Wilson disease

Personality disturbances
Tremor
Dystonia
Choreic movements
Hypokinesis, drooling
Kayser-Fleischer rings

Diagnosis of Wilson disease

- Serum ceruloplasmin
- Urinary copper
- Hepatic copper
- Hepatic histology
- Glucosuria, hemolysis
**Alpha 1 Anti-trypsin**

Associated with emphysema

Low A1A levels
Neutrophil elastase
Check Phenotype/Alleles (MM, MS, ZZ)

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**Shock Liver/ Ischemic Hepatitis**

Hypotensive event or shock situation
Marked elevation in transaminases over 1000 with rapid decline
Supportive care and optimize hemodynamics
Laboratory features of ischemic hepatitis

Intra vs Extra hepatic causes

Overproduction of bilirubin

Impaired uptake, conjugation or excretion of bilirubin

Predominantly Cholestatic Pattern (Elevated Bili)
Biliary Anatomy

Classification of jaundice

<table>
<thead>
<tr>
<th>Unconjugated hyperbilirubinemia</th>
<th>Conjugated hyperbilirubinemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increased bilirubin production</strong></td>
<td><strong>Intrahepatic disorders</strong></td>
</tr>
<tr>
<td>Hemolysis</td>
<td>Hepatocellular disease of any cause (eg, viral hepatitis)</td>
</tr>
<tr>
<td>Erythrocyte abnormality (eg, hereditary spherocytosis, G-6-PD deficiency)</td>
<td>Cholestatic disease of any cause (eg, primary biliary cirrhosis)</td>
</tr>
<tr>
<td>Extracellular abnormality (eg, hypersplenism, immunohemolytic anemia)</td>
<td><em>Metabolic disorder</em></td>
</tr>
<tr>
<td>Ineffective erythropoiesis (eg, thalassemias)</td>
<td>Dubin-Johnson syndrome</td>
</tr>
<tr>
<td>Hematoma breakdown</td>
<td>Rotor syndrome</td>
</tr>
<tr>
<td><strong>Decreased hepatic bilirubin clearance</strong></td>
<td>Benign recurrent intrahepatic cholestasis</td>
</tr>
<tr>
<td>Neonatal hyperbilirubinemia</td>
<td>Cholestasis of pregnancy</td>
</tr>
<tr>
<td>Fasting</td>
<td><em>Extrahepatic disorder</em></td>
</tr>
<tr>
<td>Gilbert's syndrome</td>
<td>Biliary tract pathology (eg, tumor or stricture)</td>
</tr>
<tr>
<td>Crigler-Najjar syndromes</td>
<td>Pancreatic pathology (eg, carcinoma)</td>
</tr>
</tbody>
</table>
Evaluation of Conjugated Hyperbilirubinemia

Liver/biliary ultrasound
CT
Nuclear medicine imaging
ERCP/PTC/MRCP
Liver biopsy

Extrahepatic Cholestasis/ Cholangitis

Choledocolithiasis (most common)
Malignancies
pancreatic head, ampullary, cholangiocarcinoma
Primary Sclerosing Cholangitis (PSC)
Chronic pancreatitis
AIDs cholangiopathy (CMV, cryptosporidium)
Extrahepatic Cholestasis

Right upper quadrant pain, fever
Mild elevation of transaminases
++ Alk phos elevation
Elevated Bilirubin
ERCP/MRCP/EUS

ERCP in extrahepatic biliary obstruction
Intrahepatic Cholestasis

TPN

Non-hepatobiliary sepsis

Paraneoplastic syndrome (Stauffer’s syndrome)

- Hodgkins, medullary thyroid CA, hypernephroma, renal sarcoma, prostate CA, T-cell lymphoma

Isolated Elevation of Alkaline Phosphatase

- Alkaline Phosphatase
  - From liver/bones/intestines
  - Third trimester pregnancy (placenta)
  - Blood type O & B after fatty meal
  - Rapidly growing adolescents
  - Normal increase by age in women
Isolated Elevation of Alkaline Phosphatase

Source:
Electrophoretic separation/fractionation

Initial testing:
Chronic cholestatic or infiltrative liver diseases if liver origin
PBC, PSC, drugs (dilantin/steroids), sarcoid, amyloid, metastatic disease, abscess

Cirrhosis

- Liver cell necrosis
- Inflammatory cell infiltrate
- Fibrosis
- Nodular regeneration which may be macronodular (alcohol), micronodular (viral) or mixed
Causes of Cirrhosis

- Alcohol
- Viral B/C
- Cryptogenic
- Primary Biliary Cirrhosis
- Hemochromatosis
- Wilsons
- Alpha 1 antitrypsin deficiency
- Autoimmune
- Sclerosing Cholangitis

Complications

- Portal Hypertension causing variceal bleed
- Splenomegally causing low platelets
- Ascites
- Encephalopathy
- SBP
- Hepatorenal syndrome
- Hepatocellular carcinoma
- Death
Varices and portal gastropathy

Large varices of stigmata of recent bleeding