Evaluation of Elevated Liver Function Enzymes and Update on Hepatitis C

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It is most often a slow process. Sometimes it can be rapid. The liver can take a beating for a long time. And then it fails.

Jaundice

Spider angiomata

Asterixis

Palmar erythema

Songs you don’t want to hear when waking up from Anesthesia

Stairway to Heaven  Led Zeppelin
Another one bites the dust  Queen
I will never Breathe again  Toni Braxton
Dust in the wind  Kansas
I am barely breathing  Duncan Sheik
I’m half the man I used to be  Pearl Jam
Knockin’ on Heaven’s door  Bob Dylan
It’s over  Boz Scaggs
No Time (Left for You)  Guess Who
You’re my favorite mistake  Sheryl Crow
Background

- No single test reveals the function of liver
- Broad array of biochemical tests
  - Aminotransferases, alkaline phosphatase, bilirubin, albumin, prothrombin time, GGT
- These tests known as liver function tests

Background

- Liver associated tests used to screen for liver disease
- Estimate severity
- Assess prognosis
- Monitor therapy
Background

- Stratification – Hepatic vs Cholestatic
- Temporal – Acute vs Chronic
- Degree – Mild vs Marked
- Ratio – AST vs ALT; AP vs ALT

Elevated liver function tests

Pattern

- Cholestatic
  - Elevated alkaline phosphate and/or total bilirubin
- Parenchymal
  - Elevated aminotransferases

Aminotransferase Levels

- Aspartate aminotransferase (AST/SGOT) found in the liver, cardiac muscles and a variety of other tissues.
- Highest level of alanine aminotransferase in liver.
- Damage to liver cell membrane results in both enzymes released into the blood.

Chronically elevated aminotransferase

Hepatic Causes
- Alcohol abuse
- Medication/substances
- Chronic hepatitis B and C
- Fatty liver
- Autoimmune hepatitis
- Hemochromatosis
- Wilson’s Disease
- Alpha-1-antitrypsin deficiency

Nonhepatic Causes
- Celiac sprue
- Inherited disorders of muscle metabolism
- Acquired muscle disease
- Strenuous exercise
Substances causing elevated aminotransferase

**Medications**
- Antibiotics: Penicillins, Ciprofloxacin, Nitrofurazone, Ketoconazole, Isoniazid
- Antiepileptic Drugs: Phenyltoin, Carbamazepine
- Inhibitors of hydroxymethylglutaryl coenzyme A reductase
- Nonsteroidal antiinflammatory drugs
- Sulfonylureas for hyperglycemia

**Herbs and Homeopathic Treatments**
- Chaparral, Chinese Herbs (Ji bu huan, Ephedra [Mahuang]), Gentian, Germander, Alchemilla (Lady’s Mantle), Senna, Shark Cartilage, Scutellaria Skullcap

**Drugs and Substance of Abuse**
- Anabolic Steroids, Cocaine, MDMA (Ecstasy), Phencyclidine (Angel Dust), Glues and Solvents (Glues containing toluene; Trichloroethylene, chloroform)

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**Diagnostic approach to acute hepatitis**

**Acute Hepatitis**
- History and physical examination (risk factors for viral hepatitis, drugs, autoimmune)

**Viral**
- Hepatitis A
- Hepatitis B
- Hepatitis C
- CMV
- EBV

**Metabolic**
- Wilson’s disease

**Autoimmune**
- Type 1: ANA, SMA
- Type 2: Anti-KLM
- Type 3: Anti-SLA

**Other**
- Congestive heart failure
- Biliary tract disease

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**Diagnostic approach to chronic hepatitis**

**Chronic Hepatitis**
- History and physical examination (risk factors for viral hepatitis, drugs, autoimmune)

**Viral**
- Hepatitis B
- Hepatitis C

**Metabolic**
- Hemochromatosis
- Wilson’s disease

**Autoimmune**
- Type 1: Alpha-1 antitrypsin deficiency
- Type 2: Steatosis (including alcohol)
- Type 3: Nonhepatic causes
Acute and Chronic Disease Burden, United States

<table>
<thead>
<tr>
<th></th>
<th>HAV</th>
<th>HBV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>New infections, 1997</td>
<td>179,000</td>
<td>205,000</td>
<td>36,000</td>
</tr>
<tr>
<td>Persons with acute infection</td>
<td>None</td>
<td>1.25 million</td>
<td>2.7 million</td>
</tr>
<tr>
<td>Deaths due to chronic liver disease</td>
<td>None</td>
<td>5,000</td>
<td>8,000 - 10,000</td>
</tr>
</tbody>
</table>

Centers for Disease Control and Prevention. Unpublished data.

Utility of Liver Biopsy

Confirm clinical diagnosis
Assess severity of necroinflammation
Role of Liver Biopsy
Evaluate possible concomitant disease
Assess fibrosis
Assess therapeutic intervention

Sent to United States for National Tour

Distinguished sponsors

Upon return to Italy
Prevalence of Chronic Liver Disorders in the United States

1. Nonalcoholic Fatty Liver Disorder (NAFLD)
2. Nonalcoholic steatohepatitis (NASH)
3. Chronic Hepatitis C
4. Alcoholic Liver Disease
5. Hemochromatosis
6. Chronic Hepatitis B

Natural History of NASH

- Mortality higher than general population (SMR: 1.34)
- 1.2% risk of progression over 15-20 years
- Significant variability in progression rate; Diabetes, high BMI associated with more rapid progression
- Cirrhosis: ~3% general population; 20-40% of pts w/BMI >35 kg/m²
- ~12-20% risk of progression over 8 years

Distribution by Cause of Newly Diagnosed Chronic Liver Disease

- 24% Alcohol
- 57% Hepatitis C
- 9% NAFLD
- 4% Hepatitis B
- 6% Other
Patients at Risk for Fibrosis Progression

<table>
<thead>
<tr>
<th>Author</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angulo et al</td>
<td>Age, obesity, diabetes, AST/ALT ratio</td>
</tr>
<tr>
<td>Marceau et al</td>
<td>Age, steatosis, fasting blood sugar, waist-to-hip ratio, BMI, diabetes mellitus</td>
</tr>
<tr>
<td>Garcia-Monson et al</td>
<td>Age, steatosis, inflammation grade</td>
</tr>
<tr>
<td>Katz et al</td>
<td>Age, BMI, ALT, triglycerides, inflammation grade</td>
</tr>
<tr>
<td>Dixon et al</td>
<td>Hypertension, ALT, C-peptide, insulin resistance</td>
</tr>
<tr>
<td>Chitturi et al</td>
<td>Female, diabetes, inflammation grade</td>
</tr>
<tr>
<td>Harrison et al</td>
<td>Age, diabetes, female, AST/ALT ratio</td>
</tr>
</tbody>
</table>

Metformin

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Dose</th>
<th>Duration</th>
<th>Insulin Sensitivity</th>
<th>Histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwimmer et al</td>
<td>Open-label</td>
<td>500 mg bid</td>
<td>6 months</td>
<td>Improved</td>
<td>No biopsy. Steatosis improved on MRA</td>
</tr>
<tr>
<td>Stengel et al</td>
<td>Randomized</td>
<td>850 mg bid</td>
<td>6 months</td>
<td>Improved</td>
<td>No significant improvement</td>
</tr>
<tr>
<td>Nar et al</td>
<td>Open-label</td>
<td>25 mg/kg</td>
<td>12 months</td>
<td>Improved</td>
<td>No significant improvement</td>
</tr>
<tr>
<td>Bugianesi et al</td>
<td>Open-label</td>
<td>Max dose 1 g bid</td>
<td>12 months</td>
<td>Improved</td>
<td>Improved (17/55 had bl nosis)</td>
</tr>
<tr>
<td>Nair et al</td>
<td>Open-label</td>
<td>Max dose 2 g bid daily</td>
<td>12 months</td>
<td>Improved</td>
<td>14 pts completed 46% improved</td>
</tr>
</tbody>
</table>

Role of Liver Biopsy in NAFLD

Arguments for liver biopsy:
- Exclude alternative causes
- Distinguish steatosis from NASH
- Estimate prognosis based on degree of fibrosis
- Determine progression of fibrosis over time

Arguments against liver biopsy:
- Good prognosis of NAFLD
- Lack of proven therapy
- Risks associated with biopsy

Geographic Prevalence of Chronic Hepatitis B May Be Impacted by Migration

- ~2 million Asians
- ~400,000 Europeans
- ~400,000 South Americans
- ~350,000 Africans

HbsAg Prevalence:
- >8% - High
- 2-7% - Intermediate
- <2% - Low

Immigration numbers summed by continent from 1996-2002


Chronic Hepatitis B

Transmission of Hepatitis B

Hepatitis B Disease Progression
### Drug resistance with hepatitis B therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegylated interferon</td>
<td>Not known to occur</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine</td>
<td>14</td>
<td>30</td>
<td>55</td>
<td>67</td>
<td>69</td>
</tr>
<tr>
<td>Adefovir</td>
<td>0</td>
<td>3</td>
<td>6</td>
<td>15-18</td>
<td>25-30</td>
</tr>
<tr>
<td>Entecavir</td>
<td>0</td>
<td>0</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>7</td>
<td>14</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

### Actuarial Survival in End-stage Liver Disease

<table>
<thead>
<tr>
<th>Years</th>
<th>Patients surviving (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>

**Historical Comparisons**

- Perrillo et al., 2001
- Weissberg et al., 1984
- De Jongh et al., 1992

### Decline in Need for Liver Transplantation

**Hepatitis B vs Hepatitis C**

<table>
<thead>
<tr>
<th>Year</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1985</td>
<td>0</td>
</tr>
<tr>
<td>1990</td>
<td>100</td>
</tr>
<tr>
<td>1995</td>
<td>200</td>
</tr>
<tr>
<td>2000</td>
<td>300</td>
</tr>
<tr>
<td>2005</td>
<td>400</td>
</tr>
</tbody>
</table>

### Therapy for Hepatitis C

**Treatment Naive Patients**

<table>
<thead>
<tr>
<th>Sustained virologic response (%)</th>
<th>Overall</th>
<th>Genotype 1</th>
<th>Genotype 2 and 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>PegIFN + 1000-1200 mg/RBV</td>
<td>52 - 53%</td>
<td>41 - 44%</td>
<td>65 - 75%</td>
</tr>
</tbody>
</table>

**From WR et al., AASLD Oral Presentation, 2007**
Liver Biopsy

- Pros
  - Determines extent of hepatitis C disease
  - Estimate prognosis
  - May help in the decision regarding therapy

- Cons
  - Potential complications such as discomfort, pain, and bleeding

Histologic Staging

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Stage 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Stage 1 Image]</td>
<td>![Stage 2 Image]</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Stage 4</td>
</tr>
<tr>
<td>![Stage 3 Image]</td>
<td>![Stage 4 Image]</td>
</tr>
</tbody>
</table>

Timeline for New Therapies

- **Phase 1**
  - ITMN 191 Protease inhibitor
  - GS-441523 Protease inhibitor
  - GS-0910 Protease inhibitor
  - RV128 Protease inhibitor
  - Revusozumab Anti-phospholipid

- **Phase 2**
  - NMC43055 Protease inhibitor
  - BMS-314 Protease inhibitor
  - CC-720 Protease inhibitor
  - TMC-001 Protease inhibitor
  - SLY-083 Direct-acting interferon

- **Phase 3**
  - Albubenon Interferon-Alpha
  - Telaprevir Protease inhibitor
  - Baceceprin Protease inhibitor
  - ITMN 191 Protease inhibitor

Specific Targets for HCV Treatment: Protein Synthesis

- **Ribosome**
- **HCV RNA**
- **Polyprotein Chain**

Switching Off the Protease Prevents Cleavage of the Polyprotein Chain, Halting Replication

Protease inhibitor binds to protease

Downstream cleavage is halted


PROVE 1: Telaprevir + Peg-IFN + RBV in Treat-Naive Patients with HCV Gen 1

Randomized, placebo-controlled, phase 2 trial

Treatment-Naive Patients Infected With HCV Genotype 1*

(Wk 12) (Wk 24) (Wk 48)

Placebo + Peg-IFN α-2a 180 μg/wk + RBV 1000-1200 mg/d
(n = 75)

TVR 750 mg q8 h + Peg-IFN α-2a + RBV (n = 79)

Peg-IFN α-2a + RBV (n = 82)

TVR 750 mg q8 h + Peg-IFN α-2a + RBV (n = 79)

24-Wk Follow-Up

24-Wk Follow-Up

SVR

SVR

*Patients were randomized to receive TVR 1250-mg loading dose or placebo.
† Patients must achieve undetectable HCV RNA at wk 4 (<10 IU/mL) and at last test before stopping therapy at 12 or 24 wk.
TVR = telaprevir.


Mean Log_{10} HCV RNA Levels from Baseline through Week 24


Telaprevir with Peginterferon and Ribavirin for Chronic HCV Genotype 1

Response Rates (ITT)

**Adverse Events Leading to Treatment Discontinuation, According to Treatment Group**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>ALL Telaprevir-Based Regimens (N = 175)</th>
<th>PHII (N = 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weeks 1–12</td>
<td>After Week 22</td>
</tr>
<tr>
<td>Any event (N of patients)</td>
<td>2 (12%)</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>Rash or pruritus</td>
<td>2 (12%)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>7 (5%)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal event</td>
<td>2 (12%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Psychiatric event (depression or anxiety)</td>
<td>4 (2%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Other events</td>
<td>7 (6%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Multiple events</td>
<td>3 (2%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>


**PROVE 1 Breakthroughs**

- Virologic breakthrough occurred in 7% (12 of 175 patients) (>1 log10)
- 9 of 12 TVR breakthroughs occurred during first 4 weeks
- 10 of 12 TVR breakthroughs occurred in patients who did not achieve undetectable HCV RNA
  - 10 patients with Genotype 1a
    - V36M and R155K
  - 1 patient with Genotype 1b
    - A156T/S


**Associated with STAT-C therapies for Hepatitis C infection**

- Increased sustained virologic response rates
- Additional side effects
- Will be used in conjunction with pegylated interferon and ribavirin
- Increasing complexity
- Viral resistance to novel agents

**Keeping your liver healthy**

- Alcohol abstinence
- Screen for complications of cirrhosis
- Get vaccinations against hepatitis A and B if naive

My Doctor said “Only 1 glass of alcohol a day”. I can live with that.
In the Immortal Words of Dr Seuss

“Will you succeed? Yes, you will indeed. (98 3/4% guaranteed)”

Dr. Seuss. “Oh, the Places You’ll Go!”. Random House, New York

Thank you