Update in Liver Disease

SGNA

April 4, 2014
Outline

• Interpretation of elevated liver chemistries
• Fatty liver disease
• Hepatitis B
• Hepatitis C
Case History

- A 45 year old non-drinking female was seen in the office for elevated LFTs----AST/ALT = 40/90. Remainder of her LFTs were normal.
- Persistent elevation for 2 years
- No complications of liver disease—no jaundice, ascites, variceal bleeding or encephalopathy
- +FmHx DM
- Exam weight 175 lbs ABP 150/94
- Centripetal obesity
- No other stigmata of liver disease
- What would you do next?
Evaluation of Mild Elevation in Transaminase Levels

• Degree of elevation is important---few diseases with AST and ALT > 1000
• Pattern of elevation is important AST vs ALT----most liver diseases ALT > AST. Some liver diseases have AST > ALT; this may also may signal the development of cirrhosis
• Review all recent and chronic medications
• Screen for ETOH use
• Hepatitis B and C serology
• Screen for hemochromatosis
• Evaluate for fatty liver
• Consider auto-immune hepatitis, A1AT deficiency, Wilson’s disease, thyroid disease, celiac disease
• Exclude muscle disorders, adrenal insufficiency
• Liver, Gallbladder and biliary tract imaging---US CT MRI/MRCP
• Consider biopsy if AST/ALT > 2 X uln
Evaluation of Elevated ALP level

1. Rule out physiologic causes
2. Determine Source GGTP
   - Abnormal
     - Likely hepatobiliary
   - Normal
     - Likely bone in origin
3. RUQ Ultrasound
   - AMA for PBC
     - AMA +
       - Normal bile ducts
       - Liver Biopsy
4. Bile duct dilation
   - MRCP/ERCP
   - Likely bone in origin
## Classification of Jaundice

<table>
<thead>
<tr>
<th>Un-Conjugated Hyper-bilirubinemia</th>
<th>Conjugated Hyper-bilirubinemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated indirect bilirubin</td>
<td>Elevated direct bilirubin</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>Intrinsic liver disease</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Stones</td>
</tr>
<tr>
<td>Porto-systemic shunts</td>
<td>Strictures/masses</td>
</tr>
<tr>
<td>Medications</td>
<td>PBC/PSC/metastatic tumor</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Infections</td>
</tr>
<tr>
<td>Congenital</td>
<td>Medications</td>
</tr>
</tbody>
</table>
CHALLENGE ACCEPTED
Non-Alcoholic Fatty Liver Disease
NAFLD
FATTY LIVER
find out what to do about it today!

90 MILLION AMERICANS HAVE NON-ALCOHOLIC FATTY LIVER DISEASE!

healthylivinghelpful.com
Fatty Liver Disease

- 25% of the US population is overweight and 11% are obese
- 70% of obese adolescents will remain obese as adults
- 400 million obese individuals worldwide (7%-40% of the population) and 1.6 billion overweight—WHO 2005—figures projected to double by 2015
- 75% of obese people may have fatty liver and up to 20% of these may have NASH (non-alcoholic steatohepatitis)
- Spectrum of disease—fat alone to fat + inflammation to fibrosis and cirrhosis
Fatty Liver Disease

- Becoming an epidemic both in the US and worldwide
- Usually but not always associated with weight gain, FmHx DM, hyper-triglyceridemia and HTN
- Important to exclude ETOH as the histologic pattern is identical
- Natural history is unclear but up to 30% may develop significant fibrosis and cirrhosis over a 20-30 year period
- Second most common indication for liver transplant in the US at the present time
Obesity Trends* Among U.S. Adults

(*BMI ≥30, or about 30 lbs. overweight for 5’4” person)
Risk Factors

- NAFLD parallels insulin resistance
- The presence of the metabolic syndrome increases the risk of NAFLD 4 fold and makes regression less likely
- DIONYSOS STUDY---NAFLD present in 94%, 67% and 25% of obese, overweight and normal weight people respectively.
- Higher waist circumference
- OSA—may be an independent risk factor— intra-hepatic hypoxia
- Genetic Factors ?
- Diet : conflicting data
- Gut-derived bacteria ? Role of co-existent small bowel bacterial overgrowth
# NAFLD—Risk Factors

<table>
<thead>
<tr>
<th>Acquired Metabolic Disorders in 38%</th>
<th>Obesity</th>
<th>Diabetes Mellitus</th>
<th>Hypertriglyceridemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Parenteral Nutrition, Rapid weight loss, Acute starvation</td>
<td></td>
<td></td>
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<tr>
<td>Surgery</td>
<td>Jejunoileal Bypass</td>
<td>Extensive Small Bowel Loss</td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td>Corticosteroids; Estrogens</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amiodarone</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Methotrexate; Tamoxifen</td>
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<td></td>
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<tr>
<td></td>
<td>Diltiazem; Nifedipine</td>
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<td></td>
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<tr>
<td>Occupational Exposures</td>
<td>Organic Solvents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Wilson's dis, Abetalipoproteinemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Jejunal diverticulosis</td>
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</tr>
</tbody>
</table>
Metabolic Syndrome

• Multiple different definitions

• Essential components
  waist > 37 in males/ 31 in in women
  evidence of insulin resistance
  low HDL cholesterol < 40 men < 50 women
  elevated triglycerides > 150
  HTN > 130/85
Socio-demographic Differences in NAFLD Prevalence

• Initial studies revealed a higher prevalence in females; more recent studies with equal sex distribution
• Twice as common in post vs pre-menopausal women
• Increases with age
• Ethnic differences—African Americans with more SQ and less visceral fat than Hispanics and Caucasians (high frequency of obesity and Type 2 DM). Highest incidence in Asian Indian men.
Ethnic Variation of NAFLD on Imaging Studies

Lazo, M   Seminars in Liver Disease 2008

- Asain: 45,991
- USA-Europe: 5606
- Middle East: 460

%
Bariatric population\textsuperscript{1}

- 91\% (85\%-98\%) Fatty liver
- 37\% (24\%-98\%) NASH
- 1.7\% (1\%-7\%) Cirrhosis

\textsuperscript{1}Machado, J Hepatol, 2006
How can we predict advanced disease?

• Diagnosis of advanced disease can be difficult—important to be able to differentiate simple steatosis from NASH and also the presence or absence of fibrosis.
  – No serum marker or combination prospectively validated—various non-invasive blood tests and scoring systems proposed including age, sex, HTN, DM, Insulin resistance, AST/ALT, Plts, TG, TB, alpha 2 macroglobulin, haptoglobin
  – No radiological modality can reliably distinguish NASH from simple steatosis—US/CT/MRI/MR-spectroscopy appears to be the most promising
  – Clinical predictors of advanced disease not reliable enough
Advanced liver disease in patients with normal ALT

- Advanced fatty liver disease:
  - 25/81 (30%)
  - Cirrhotic Patients - 60%

- Compared to those with elevated ALT:
  Those with normal ALT had increased incidence of DM and advanced disease

- Clinical and histologic spectrum is equivalent \(^1,^2\)

NAFLD increases cardiovascular risk independent of the metabolic syndrome

- 10 yr incidence of cardiovascular events moderately increased in NAFLD\(^1\)
- Should discovery of fat on US prompt screening for and treatment of cardiovascular disease risk factors?

Increased carotid plaque formation in NAFLD

Decreased survival in patients with NAFLD


10y follow-up

**Observed** - 77%

**Expected** - 87%

p<0.005
NAFLD—Symptoms

- Ascites
- GI bleeding
- Pruritus
- Edema
- RUQ pain
- Fatigue
- Asymptomatic

Prevalence (%)
Obesity

All fat is not created equal

Visceral fat predominates

Subcutaneous fat predominates
Liver Biopsy

• Allows estimation of disease severity and allows prognostication
• Sampling variability
• Specific histological scoring system in place
• Fibrosis more likely — age > 50, +DM, ALT > 2 X UNL
• Consider biopsy in patients with peripheral stigmata of liver disease, thrombocytopenia, age > 45, abnormal iron studies, DM, significant obesity and splenomegaly
• Histologic progression most likely in patients with baseline inflammation.
• Histology may improve or remain stable in up to 40% of patients over a 5 year period
The continuum of NAFLD

Simple steatosis

Steatohepatitis/NASH

Steatohepatitis + fibrosis

Cirrhosis

Liver failure

Hepatocellular carcinoma

? Innocent Bystander
Does what you eat matter?

Weapons of mass destruction
The New McDonalds Mini-Meal
Practical Recommendations for Lifestyle Modification

• 30-45 mins exercise three times weekly
• Goal is to improve metabolism and improve sense of well-being
• Limit on-screen time
• Focus on healthy eating not dieting
• Protein containing breakfast
• Avoid fasting
• Eliminate sugar sweetened beverages
• Avoid trans-fats
EXERCISE
Welcome to America.
Treatment

• Weight loss—intentional/ bariatric surgery
• Vitamin E and C
• Metformin
• Pioglitazone / rosiglitazone
• Probucol / betaine/ statins / AT-II inhibitors
• Ursodiol
• Pentoxifylline
• Orlistat / silbutramine / rimonabant / exenatide

No FDA-approved drug treatment for fatty liver
Laparoscopic Adjustable Band

- Purely restrictive
- Lower Morbidity / Mortality
- Faster Recovery
- Easy adjustability
- Less long term data
Gastric Bypass + Roux-en-Y

- **Restrictive**
  - Gastric pouch
  - Bypassed portion of stomach

- **Malabsorptive**
  - Duodenum
  - Roux limb
  - Common limb
# Short-Term Weight Loss after Bariatric Surgery

<table>
<thead>
<tr>
<th>Operation</th>
<th>Excess weight loss %</th>
<th>Time in yrs for wt stabilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric Bypass</td>
<td>60-85</td>
<td>1-1.5</td>
</tr>
<tr>
<td>Adjustable gastric band</td>
<td>45-55</td>
<td>2</td>
</tr>
<tr>
<td>Sleeve Gastrectomy</td>
<td>55-80</td>
<td>1-1.5</td>
</tr>
</tbody>
</table>
Liver Transplantation

UNOS Listing for Cryptogenic/NASH and HCV cirrhosis (2002-2006)

Wait List Additions per year

- Cryptogenic/NASH
- HCV

Liver Transplantation
"Big Picture" Liver Fact

Every year, approximately 15,000 Americans die from liver cancer or chronic liver disease associated with viral hepatitis.

Source: CDC (www.cdc.gov/hepatitis/hepawarenessmonth.htm)
Hepatitis B
Global Impact of Hepatitis B

2 billion with past/present HBV infection

15-40% develop cirrhosis, liver failure or HCC

350–400 million with chronic hepatitis B

~1 million/year die from HBV-associated liver disease

Global Patterns of Chronic HBV Infection

• **High** (>8%): 45% of global population
  – lifetime risk of infection >60%
  – early childhood infections common

• **Intermediate** (2%-7%): 43% of global population
  – lifetime risk of infection 20%-60%
  – infections occur in all age groups

• **Low** (<2%): 12% of global population
  – lifetime risk of infection <20%
  – most infections occur in adult risk groups
Hepatitis B Case

• 44 year old Vietnamese male seen in the clinic for elevated LFTs---AST/ALT = 76/223
• Mother with hepatitis B
• 2/4 siblings hepatitis B carriers
• No complications of liver disease
• Exam unremarkable
• High level of viremia HBV-DNA ? 320,000,000 IU/ML
• US liver normal. Alpha-fetoprotein normal
Disease Progression Occurs in 15% to 40% of Chronic HBV Patients

*HBV is the 6th leading cause of liver transplantation in the United States.

REVEAL-Incidence of Cirrhosis Increases with Increasing Baseline Serum HBV DNA Level


* p < 0.001 test for trend
Screening for Hepatitis B

- High risk and low risk countries
- In the US—universal vaccination at birth and catch-up in HS or College
- Household HBV contacts
- IVDA, prisoners, MSM, multiple sexual partners
- Patients with chronically elevated LFTs
- Patients with chronic liver disease
- All pregnant women
- Dialysis patients
- All patients undergoing immunosuppressive therapy
Hepatitis B Vaccination and Prevention of Hepatocellular Carcinoma

• Universal HBV newborn vaccination in Taiwan since 1984—1958 pts with HCC(6-29)--64 cases of HCC in vaccinated pts vs 444 cases in unvaccinated pts
• Risk of HCC was decreased 70% in pts vaccinated at birth
• In vaccinated pts risk of HCC was increased with an incomplete vaccination series and in mothers who were HBsAg+

J NCI Sept 2009
Health Care Workers (HCW) and Viral Hepatitis Exposure Risk

• Most commonly in the OR and in patient rooms
• 40% occur in RNs and 12% in MDs
• Increased with long work hours and lack of sleep—risk increased three-fold
• Residents typically do not report needle-sticks
• Occurs with syringes > scalpels
• Only 75% of HCWs have received HBV vaccine
• Hepatitis B surface antibody production lower in HCW
# Health Care Workers and the Risk of Viral Hepatitis

<table>
<thead>
<tr>
<th></th>
<th>Hepatitis B</th>
<th>Hepatitis C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seroprevalance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General population</td>
<td>0.42%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Seroprevalence HCW vs general population</td>
<td>Increased</td>
<td>Similar</td>
</tr>
<tr>
<td>Percutaneous Risk</td>
<td>6-30%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Mucosal risk</td>
<td>Risk ND</td>
<td>0.09%</td>
</tr>
<tr>
<td>Non-intact skin</td>
<td>Risk ND</td>
<td>&lt; 0.1%</td>
</tr>
<tr>
<td>Viral particles/ml of serum</td>
<td>100-100,000,000</td>
<td>1-1,000,000</td>
</tr>
</tbody>
</table>
Hepatitis B and C Outbreaks in Non-Hospital Settings in the US

- 33 outbreaks between 1998 and 2008
- 12 in OP clinics, 6 in HD centers 13 in long-term care facilities and 2 in GI Labs, the most recent in Las Vegas
- Total of 448 cases of new HBV(173pts) and HCV(275pts) infection—no cases of HIV
- Patient to patient transmission occurred in all cases through poor infection control and inadequate aseptic and sterilization techniques

Thompson et al Ann Int med 2009
Treatment of Hepatitis B

- HbSag +
- Active viremia HBV-DNA level > 2,000-20,000 IU/ml
- Elevated LFTs
- HbeAg + or HbeAb +
- Active inflammation on liver biopsy
Evolution of Approved HBV Therapy Over Time

- Interferon alfa-2b (1990)
- Lamivudine (1998)
- Adefovir (2002)
- Peginterferon alfa-2a
  - Entecavir (2005)
  - Telbivudine (2006)
- Tenofovir (2008)
### Treatment of Chronic Hepatitis B in 2014: Efficacy Data

<table>
<thead>
<tr>
<th>Drug</th>
<th>HBeAg (+) Patients</th>
<th>HBeAg (-) Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBeAg Seroconversion at Yr 1, %</td>
<td>HBV DNA Negative at Yr 1, %</td>
</tr>
<tr>
<td>Interferon alfa</td>
<td>~ 18</td>
<td>37</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>18</td>
<td>40-44</td>
</tr>
<tr>
<td>Adefovir</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>Entecavir</td>
<td>21</td>
<td>67</td>
</tr>
<tr>
<td>Peginterferon alfa-2a</td>
<td>27</td>
<td>25</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>23</td>
<td>60</td>
</tr>
<tr>
<td>Tenofovir†</td>
<td>21</td>
<td>76</td>
</tr>
</tbody>
</table>

*Interferon and lamivudine: hybridization assay; adefovir, entecavir, and peginterferon: PCR assay.

†Licensed for treatment of HIV infection; under review by FDA for treatment of chronic hepatitis B.
# Post-HBV Exposure Prophylaxis

<table>
<thead>
<tr>
<th></th>
<th>HBsAg + Source</th>
<th>HBsAg - Source</th>
<th>Unknown HBV status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unvaccinated</td>
<td>HBIG and HBV vaccination</td>
<td>HBV vaccination</td>
<td>HBV vaccination</td>
</tr>
<tr>
<td>Known responder</td>
<td>No treatment</td>
<td>No treatment</td>
<td>No treatment</td>
</tr>
<tr>
<td>Known non-responder</td>
<td>HBIG and HBV re-vaccination</td>
<td>No treatment</td>
<td>If high-risk give HBIG and HBV vaccination</td>
</tr>
<tr>
<td>Ab response unknown</td>
<td>Test for HBsAb and treat accordingly</td>
<td>No treatment</td>
<td>Test for HBsAb and treat accordingly</td>
</tr>
</tbody>
</table>
Hepatitis C
Hepatitis C Case

• A 52 year old ex-IVDA seen in the office for asymptomatic elevation in AST/ALT = 89/167. Remainder of LFTs all normal
• No drug use for 25 years.
• No complications of liver disease
• Used to drink heavily in the past and now 3-4 drinks per week
• Exam unremarkable
• What next?
Prevalence of HCV

**Worldwide**

- 170 million (3%)

**United States**

- Anti-HCV positive: 3.9 million (1.8%)
- HCV RNA positive: 2.7 million (1.4%)

> 14,000 deaths annually in the US

Causes of Hepatitis C

- Sharing needles and other equipments
- Mother to Baby Transmission
- Tattooing
- Blood Transfusion
- Sex with infected partner
Sources of Infection for Persons With Hepatitis C

- Injecting drug use: 60%
- Sexual: 15%
- Transfusion (before screening): 10%
- Occupational: 4%
- Other: 1%
- Unknown: 10%

* Nococomial; heterogenic; perinatal

Source: Centers for Disease Control and Prevention
Hepatitis C
Testing baby boomers saves lives

3 Million | 3 in 4
About 3 million adults in the US are infected with the hepatitis C virus, most are baby boomers.
Up to 3 in 4 people who are infected don’t know they have hepatitis C so they aren’t getting the necessary medical care.

1945–1965
Baby boomers, anyone born from 1945 through 1965, should get tested for hepatitis C.
BORN FROM 1945 TO 1965?

AMERICANS BORN DURING THESE YEARS HAVE THE HIGHEST RATES OF HEPATITIS C.
U.S. HCV Treatment Cascade

Overall: 3.2 million of U.S. population with chronic HCV

(Holmberg et al., "Hepatitis C in the U.S." N Engl J Med 2013; 368: 1859-1861)
HCV Life Cycle

1. Viral entry
2. Endocytosis, cell entry
3. Release of positive strand RNA into cytoplasm
4. Translation of RNA into protein
5. Polyprotein processing
6. RNA replication
7. Viral packaging
8. Release of virus

Illustration courtesy of Alison Jazwinski, MD.
Rate of Chronic HCV Infection in the US Highest Among Young African-American Adults
Incidence of Acute Hepatitis C Has Declined in the U.S.

Surrogate tests on donors

Anti-HCV test

Decline among injection drug users

Cases per 100,000

Year

CDC, 1995
Viral Hepatitis and Hepatoma in the United States

- HBV most frequent in Asians
- HCV most frequent in whites and blacks

(N=691)
Patients with chronic HCV infection have significantly more lost days from work and more days of short-term disability compared with employees without chronic HCV infection.

Hepatitis C Increases all Cause Mortality

- NHANES III Database
- 16,509 HCV patients seen from 1988-1994 and followed up until 2006 compared to control group with no HCV
- Overall mortality increased 2.4 fold compared to non-infected patients.
- Liver related mortality increased 25 fold

El Kamary et al  J Clin Inf Dis 201
HCV Infection → Chronic Hepatitis → Cirrhosis → HCC

- HCC: 1% (1%-3%/year)
- Cirrhosis: 15% (10%-30%)
- Chronic Hepatitis: 90% (60%-95%)
- HCV Infection: 100%

Goodgame B, et al., Am J Gastroenterol 2003
Hepatitis C Predicting Disease Severity

- Clinical—+/- symptoms, complications of liver disease
- Laboratory testing—Bilirubin, albumin, INR, Creatinine, Platelet count, Fibrosis markers
- Imaging—US, CT, MRI, Fibroscan
- Biopsy
Hepatic Fibrosis

Staging according to Metavir Score

F1
Portal fibrosis

F2
Portal fibrosis with few septa

F3
Septal fibrosis

F4
Cirrhosis
To Treat or Not to Treat: Pre-2013
A Constellation of Considerations

- Genotype: virus, patient (IL28B)
- Personal plans (marriage, pregnancy)
- Patient mindset
- Extrahepatic features (fatigue, EMC, PCT)
- Histologic stage
  20%+ lifetime risk of cirrhosis
- ALT
- HIV coinfection
- Duration of infection
- Family and other support
- Occupation
- Contraindications & comorbidities; insulin resistance
What Are the Key Elements of an Ideal HCV Regimen?

- **Highly Effective**: High efficacy in traditionally challenging populations (ie, nulls, cirrhosis)
- **Safe and Tolerable**: Few or easily manageable adverse effects
- **All Oral**: PegIFN/RBV replaced with alternate backbone with low chance of resistance
- **Pan-Genotypic**: Regimen can be used across all genotypes
- **Simple Regimen**: Short duration, simple, straightforward stopping rules
- **Easy Dosing**: Once daily, low pill burden

[Diagram with boxes for each element]
Evolution of DAAs

a. Virus binding and internalization
b. Cytoplasm release and uncoating
c. IRES-mediated translation and polyprotein processing
d. Packaging and assembly
e. Virion maturation and release

HCV Therapy: Past, Present and Future

- Interferon
- Ribavirin
- Pegylated interferons
- Proof of concept for DAA (PI)
- Suppression of HCV with DAA combination (PI + NI)
- Curability of HCV without interferon
- Telaprevir and boceprevir
- Frequent curability of diverse populations without IFN
- Potential approval of other DAAs with IFN (eg, faldaprevir)


- Approval of simeprevir and sofosbuvir with IFN
- First approved IFN-free therapy: SOF + RBV for GT2/3

IFN-free DAA combinations (GT1)
Efficacy With Simeprevir + P/R in Tx-Naive GT1 Patients: Phase III Trials

- SMV + P/R for 12 wks followed by 12-36 wks of P/R (placebo control)

Efficacy With Sofosbuvir + P/R in Tx-Naive GT1/4/5/6 Patients: Phase III Trials

- Single-arm study of sofosbuvir + P/R for 12 wks

SVR12 According to GT

- GT1: 89% (261/292)
- GT4: 96% (27/28)
- GT5/6: 100% (7/7)

SVR12 According to Fibrosis Level

- No Cirrhosis: 92% (252/273)
- Cirrhosis: 80% (43/54)

12-Wk IFN-Free Regimens in GT1 Treatment-Experienced Patients

**AVIATOR**

ABT-450/RTV + ABT-267 + ABT-333 + RBV
12 Wks

- SVR12 (%): 93
- N = 45

**ELECTRON**

- SOF/ledipasvir FDC 12 wks
- SOF/ledipasvir FDC + RBV 12 wks
- SOF/ledipasvir FDC + GS-9669 12 wks

- SVR12 (%): 70
- N = 10
- SVR12 (%): 100
- N = 10
- SVR12 (%): 100
- N = 25
- SVR12 (%): 100
- N = 25

Efficacy of Simeprevir and/or Sofosbuvir in Previous Null Responders


Phase IIb Trial of Simeprevir + PegIFN/RBV

- Placebo + pegIFN/RBV
- SMV 100 mg + pegIFN/RBV
- SMV 150 mg + pegIFN/RBV

SVR12 (%)

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<thead>
<tr>
<th>Fibrosis</th>
<th>24 Wks</th>
<th>12 Wks</th>
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<tbody>
<tr>
<td>F0-2</td>
<td>58</td>
<td>66</td>
</tr>
<tr>
<td>F0-3</td>
<td>22</td>
<td>38</td>
</tr>
<tr>
<td>F0-4</td>
<td>23</td>
<td>31</td>
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SVR24 (%)

<table>
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<tr>
<th>Genotype</th>
<th>24 Wks</th>
<th>12 Wks</th>
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<tbody>
<tr>
<td>7</td>
<td>33</td>
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<td>1a</td>
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<td>13</td>
<td>15</td>
<td>100</td>
</tr>
</tbody>
</table>

Phase IIb Trial of Simeprevir + PegIFN/RBV

- SMV 100 mg + pegIFN/RBV
- SMV 150 mg + pegIFN/RBV

SVR4 (%)

<table>
<thead>
<tr>
<th>Fibrosis</th>
<th>24 Wks</th>
<th>12 Wks</th>
</tr>
</thead>
<tbody>
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How Far Are We?

One Size . . . Fits All?

Same treatment regardless of fibrosis level, previous treatment experience, or HCV genotype?
Are We Moving to Primary Care?

One size fits all may be critical

Project ECHO Web site.
Should all patients with Hepatitis C be treated ???
THIS
WILL NOT END WELL