Top Hepatology Findings/Papers of 2013

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FGS/ACG meeting
3/28/14

Outline

• HCC
• HCV (non treatment)
• Non-invasive fibrosis measurement
• NAFLD
• HBV
• Cirrhosis
Global Burden of Disease Study 2010: Causes of Death From Chronic Liver Disease

Global 2010 vs USA 2010

Increase in liver-cancer deaths (past 20 years):
- Globally (from 1.25 to 1.75 million/year); USA (45,000 to 70,000/year).


Meta-analysis: Risk of HCC in HCV Pts With Advanced Fibrosis Following SVR

- 1000 patients with bridging fibrosis or cirrhosis who achieved SVR following IFN-based HCV therapy followed for median of 5.7 yrs
- Cirrhotics at greatest risk of HCC following SVR
  - Still need HCC screening!

### Age as a Risk Factor for HCC Following SVR in HCV Pts With Advanced Fibrosis

- HCC risk increased with age; highest for those > 60 yrs

**8-Yr HCC Rate, % (95% CI)**

- > 60 yrs of age: 12.2% (5.3-19.1)
- 45-60 yrs of age: 9.7% (5.8-13.6)
- < 45 yrs of age: 2.6% (0.0-5.5)


### Update of HCC Surveillance Guidelines AASLD

- Surveillance is recommended (q 6 month ultrasound)
  - HBV
    - Cirrhosis
    - Asian male > age 40; female > age 50
    - Family history of HCC
    - African/North American blacks
  - All patients with Cirrhosis
    - HCV, PBC, Genetic hemachromatosis, A1AT
  - Surveillance benefit uncertain
    - HBV carriers age < 40 male and age < 50 female
    - HCV-stage 3 fibrosis
    - Non-cirrhotic NAFLD
Primary Care Setting: HCV Persons Unidentified by Risk-Based Screening

- Cross-sectional study (2005-2010)
  - 4 large primary care health systems
  - ≥18 years of age
  - Median follow-up: 5 months
  - Multiple imputation used to predict HCV results for patients not tested for HCV

- Newly enrolled patients (n=209,076)
  - Tested for HCV: 8.4%
  - Predicted HCV prevalence: 2.9%
  - Total HCV cases: 6005
    - Proportion unidentified: 81%

<table>
<thead>
<tr>
<th>Results</th>
<th>Patients (n=209,076)</th>
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<tbody>
<tr>
<td>Tested for HCV (%)</td>
<td>8.4</td>
</tr>
<tr>
<td>Number HCV positive</td>
<td>1115 (0.53%)</td>
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Predictors of HCV positivity (adjusted odds ratio)
- Born 1945-1965: 4.4*
- Male gender: 1.4*
- Black: 1.0*
- Hispanic: 1.9*
- Elevated ALT: 4.8*
- IDU: 6.3*

- Predicted HCV prevalence: 2.9%
- Total HCV cases: 6005
  - Proportion unidentified: 81%


Opt-Out HCV Screening of Baby Boomers in Urban Emergency Department

- University of Alabama ED
  - Interim report: screening from 9/3/13 to 10/17/13

- Screening population and methods
  - Born between 1945-1965 and medically and surgically stable
  - Verbal questionnaire administered by ED nurse
  - Anti-HCV testing provided results within 29 minutes
  - Quantitative HCV RNA testing followed

**Opt-Out HCV Screening in ED: High Rates of HCV Ab+ Individuals Identified**

- **1287 (74.8%)** unaware of HCV status
- **1148 (90.8%)** accepted test offering
- **984 (85.7%)** anti-HCV tests performed
- **866 (88.0%)** anti-HCV-, **118 (12.0%)** anti-HCV+
- **27 (27.5%)** HCV RNA-, **71 (72.5%)** HCV RNA+

### Baseline Factor

<table>
<thead>
<tr>
<th>Insurance</th>
<th>HCV Ab+, % (n/N)</th>
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<tbody>
<tr>
<td>Uninsured</td>
<td>17 (35/210)</td>
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<tr>
<td>Public/Medicaid</td>
<td>17 (35/203)</td>
</tr>
<tr>
<td>Medicare</td>
<td>11 (33/315)</td>
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<tr>
<td>Private</td>
<td>4 (10/226)</td>
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<table>
<thead>
<tr>
<th>Race</th>
<th>HCV Ab+, % (n/N)</th>
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<tbody>
<tr>
<td>White</td>
<td>13 (67/515)</td>
</tr>
<tr>
<td>Black</td>
<td>11 (50/454)</td>
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<table>
<thead>
<tr>
<th>Sex</th>
<th>HCV Ab+, % (n/N)</th>
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<tbody>
<tr>
<td>Female</td>
<td>8 (39/505)</td>
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<tr>
<td>Male</td>
<td>17 (79/479)</td>
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- Program projected to screen 7872 people and identify 864 HCV Ab+ individuals over 1 yr

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**Non-invasive Fibrosis Imaging Tests**

- **Rationale:** Collagen deposition associated with fibrosis produces a lattice-like framework that imparts rigidity
  - Liver stiffness as a marker for fibrosis
- **Tests**
  - Ultrasound elastography
  - Magnetic resonance elastography
- **Pros**
  - High accuracy for diagnosis of advanced liver disease
  - Correlates with clinical consequences of portal HTN
- **Cons**
  - Limited ability to discriminate low-intermediate stages of fibrosis
Ultrasound based Transient Elastography (FibroScan)

- The more stiff/fibrotic the liver the faster the wave propagates.
- Liver Biopsy 1/50,000 of liver, Fibroscan 1/500 of liver
- Is quick, painless and reproducible


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Diagnosis Accuracy of Liver Stiffness in Chronic Viral Hepatitis

- Large US cohort (n=907; HCV 93%, HBV 7%)
  - Phase 1 (n=188/237 evaluable biopsy/FSCAN)
  - Phase 2 (n=560/670 evaluable biopsy/FSCAN)
  - FSCAN/biopsy failure: 10.4%/7.9%
- Liver stiffness has high accuracy for staging >F2 fibrosis
- AUC 0.91
  - Elastography excellent for exclusion of cirrhosis
- Higher BMI can affect cutoffs
  - XL over M probe preferred

<table>
<thead>
<tr>
<th>Stage</th>
<th>Phase 1</th>
<th>Phase 2*</th>
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<tbody>
<tr>
<td>&gt;F2</td>
<td>81.9 (72.0-89.5)</td>
<td>79.0 (70.0-86.4)</td>
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<tr>
<td></td>
<td>57.9 (52.7-63.0)</td>
<td>74.9 (68.0-80.9)</td>
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<tr>
<td>&gt;F3</td>
<td>88.3 (77.4-95.2)</td>
<td>81.9 (73.4-87.6)</td>
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<tr>
<td></td>
<td>71.8 (64.2-77.6)</td>
<td>80.1 (76.0-84.3)</td>
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<tr>
<td>F4</td>
<td>84.2 (78.7-94.0)</td>
<td>86.0 (79.4-81.1)</td>
</tr>
<tr>
<td></td>
<td>75.9 (64.0-83.6)</td>
<td>85.1 (82.1-98.6)</td>
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*P<0.003 versus phase 1.

FSCAN: FibroScan.
**Fibrotest**

- Alpha 2 macroglobulin
- Haptoglobin
- Apolipoprotein 1
- Total bilirubin
- GGT
- ALT

- 0 - 0.10 Probability of fibrosis < 10%
- 0.10 - 0.60 Liver biopsy recommended
- 0.60 - 1.00 Probability of fibrosis > 90%

*Imbert-Bismuth, Lancet 2001*

**FibroTest Combined with FibroScan**

- Prospective comparison of transient elastography, FibroTest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C.

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>Recommend algorithm (from author)</th>
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<tbody>
<tr>
<td>- Fibroscan seemed able to assess liver fibrosis with a performance similar to that of FibroTest.</td>
<td></td>
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<tr>
<td>- The combined use of Fibroscan and FibroTest to evaluate liver fibrosis could avoid a biopsy procedure in most patients with chronic hepatitis C</td>
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- Castera et al, Gastroenterology 2005
Fibrosis Stage, But Not NAS Is Predictive of Disease-Specific Mortality in NAFLD After 33 Years of Follow-Up

• Overview:
  – Evaluate the risk for all-cause and disease-specific mortality in biopsy proven NAFLD with matched controls without NAFLD
• Results
  – Mortality rate of 42% in NAFLD pts vs 34% controls
    • NAFLD pts 26% more likely to die
      – Cause: CVD, HCC, cirrhosis, infection
    – NAFLD Activity Score (NAS) did not predict mortality
    – Stage 0-2, regardless of NAS did not have increased mortality
    – Stage 3-4 and any NAS was associated with increased mortality
      • HCC (HR 16.9)
      • CVD (HR 4.6)
• Conclusion
  – Identify and treat NASH pts with advanced fibrosis

Ekstedt M et al. LB-5. AASLD 2013

Algorithm for performing liver biopsy in patients with NAFLD

Elevated ALT levels in the absence of alcohol or other chronic liver disease

Fatty liver on imaging (no substantial alcohol use)

Fatty liver index positive

Probable NAFLD

Risk factors or red flags
• Age ≥50 years
• Hispanic
• BMI ≥30
• Postmenopausal women

If ≥2 red flags, consider liver biopsy initially
If <1 red flag, optimize metabolic status and follow-up in 6 months

Torres, D. M. & Harrison, S. A. (2013) Predictive value of ALT levels for NASH and advanced fibrosis
Modest Alcohol Consumption Decreases the Risk of Having Nonalcoholic Fatty Liver Disease: A Meta-analysis of 43,175 Individuals

- **Background:** generally recommended that pts with liver disease refrain from ETOH
- **Results:**
  - Protective effect of moderate ETOH consumption, which was associated with a 30% lower risk for developing NAFLD and less severe histological disease
  - Protective effect greater in women (53% reduction)

Sookoian, S et al. Hepatology 2013

A Prospective Double-Blind Randomized Placebo Controlled Trial of Carvedilol for Early Prophylaxis of Esophageal Varices in Cirrhosis

- **Goal:**
  - To document the efficacy of carvedilol (Coreg), a non-cardiac-selective vasodilating B-blocker in the prevention of progression of esophageal varices
- **Methods:**
  - 175 pts with small varices (<5mm) randomized to Carvedilol (mean 12mg/d) vs placebo for 12 months
- **Results**
  - 19% of carvedilol and 20% of placebo pts developed large esophageal varices
  - No sig differences in HVPG between 2 groups at 12 mo
  - 8% AES for carvedilol vs 1.5% placebo
- **Conclusion**
  - Carvedilol was not effective in preventing the growth of small varices

Bhardwaj A et al; Hepatology 2013
Treating Muscle Cramps In Patients With Cirrhosis

- Background: very common in cirrhosis (22-88%)
- Treatment options:
  - Vit E 300 mg tid
  - Zinc 220 mg bid
  - Taurine (3gms daily)
    - Essential a.a found in most energy drns
  - Branched chain amino acids
- Avoid
  - Quinine sulfate: associated with thrombocytopenia, hemolysis, and cardiac arrhythmias


HBV Reactivation With Rituximab in Pts With Hematologic Malignancies

- Study of HBsAg-negative anti-HBc-positive pts receiving rituximab-containing chemotherapy (N = 62)
  - Baseline HBV DNA undetectable (< 10 IU/mL)
  - HBV DNA monitored monthly during chemo
- 24.2% of patients experienced HBV reactivation within 9 mos
  - Reactivation occurred early (86.7% within 6 mos)
- Conclusion: either monitor HBV or use prophylaxis

- Lower baseline anti-HBs levels associated with subsequent HBV reactivation ($P = .015$)

Phase 3 studies: 7-Year Tenofovir Treatment for Patients With Chronic HBV

**Study 103**

HBeAg-Positive Treatment-Naïve Study 102
HBeAg-Negative Lamivudine naïve or experienced

<table>
<thead>
<tr>
<th>48 Weeks Double-Blind</th>
<th>7 Years Open-Label</th>
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<tr>
<td>Tenofovir DF 300 mg</td>
<td>Tenofovir DF 300 mg</td>
</tr>
<tr>
<td>Adefovir 10 mg</td>
<td>Tenofovir DF 300 mg</td>
</tr>
</tbody>
</table>

*Pretreatment liver biopsy. Other eligibility criteria: age 18-69 years, compensated liver disease, HBV DNA >10^6 copies/mL, ALT ≥2 x ULN and <10 x ULN, Knodell necroinflammatory score ≥3, seronegative for HIV, HDV, and HCV.

†If HBV DNA >400 copies/mL, option to add emtricitabine to tenofovir DF in a fixed-dose tablet.


Study 103 (HBeAg Positive):
HBV DNA <400 Copies/mL (OT)

Impact of Tenofovir on Fibrosis Response

- Fibrosis score either improved (≥1 unit decrease) or did not change in 96% of patients with paired biopsies
- HBV DNA <400 copies/mL: 98% (on-treatment)

Regression of Change in Ishak Fibrosis Scores Among Cirrhotics

- Patients with cirrhosis (Ishak fibrosis score ≥5) with paired baseline and year 5 biopsies (n=96)
- Year 5
  - Cirrhosis reversed: 74%
  - ≥2 point decrease in Ishak fibrosis score: 73%
  - No change: 25%

Study 103 and 102: Virologic and Biochemical Suppression at Year 7

- No resistance to tenofovir was detect
- Virologic breakthrough was rare (<1.0%)
  - Attributed to documented non-adherence in the majority of cases
- Tenofovir was well tolerated
  - 75% of patients entering open-label phase remained on study at year 7
  - Discontinuations due to adverse events: 2.2%
  - Renal events were rare during open-label phase: 1.7%
    - 1 discontinuations due to blood creatinine increase
  - No evidence of loss in bone mineral density (by DXA) during follow-up years 4 to 7


Coffee and Liver Disease

- 500 epidemiologic studies suggest that moderate coffee consumption (2-3 cups/day)
  - Reduction in HCC (43% from 2 meta-analyses)
  - Decrease fibrosis and cirrhosis
  - Protection from NAFLD
    - Reduction in type II diabetes

Conclusion

• General advice for liver disease patients and my philosophy on how to be a popular consultant
  – Stay thin and exercise
  – Drink 2 cups of coffee/day
  – Drink 1-2 glasses of red wine/day
  – Vit E 400-800 IU/day
  • Liver disease and dementia (Alzheimers)