NAFLD in 2016:
New opportunities in the (not so distant?) future

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High Impact Hepatology
10 December 2016
Disclosures

• I have no pharmaceutical disclosures pertinent to this talk.
• I will discuss off label use of drugs.
• The *majority* of these slides were prepared with the help of Dr. Sid Barritt who does the majority of the NASH research at UNC.
Learning Objectives

• By the conclusion of the lecture, the learner should be able to:
  
  – Discuss the current therapies for non-alcoholic fatty liver disease in the United States
  
  – Discuss mechanisms of action for potential new therapies for non-alcoholic fatty liver disease
  
  – Discuss implications of the growing population of patients with non-alcoholic fatty liver disease
Roadmap

• Where we’ve been
  – Lifestyle modification

• Where we are now
  – Conflicting alcohol data
  – AASLD 2016
  – East vs. West

• Where we are going
  – Clinical trials
WHERE WE’VE BEEN

Lifestyle modification
Clinical Questions

• What are the dietary recommendations for my patients with NAFLD?

• What are the exercise requirements for patients with NAFLD?
Doc, I know I need to eat better, but which diet is the best?

- Multiple studies have examined different diets
  - All show some degree of biochemical or histological improvement
    - Mediterranean diet (high monounsaturated fats)
    - Reduced calorie high carb/low fat
    - Reduced calorie low carb (Adkin’s diet)
    - Fish oil supplements?
    - Reduction in trans fats and high fructose corn syrup
  - Sustained weight loss of 7-10% independent of diet is ultimate goal
    - Newer data show continued benefit through 20% weight reduction

Barritt, AGA Perspectives, 2013
Is there a diet that causes fatty liver?

• ~1900 children from Avon- Longitudinal Study of Parents and Children in SW England
  – Other etiologies of liver disease excluded
  – Dietary surveys, labs, transient elastography and ultrasound measured
  – Caloric intake and macronutrient intake measured
  – Hepatic fat associated with total energy intake rather than macro nutrient composition
  – “Methinks thou doth eat too much!”
Do I really need to go to the gym?

• YES!

• Most clinicians agree that diet should be accompanied by modest exercise with a goal of 30-60 minutes of exercise 3-5 x per week

Aerobic vs. anaerobic exercise?

• Study of 375 people in Israel found that leisure time physical activity inversely assoc w/ NAFLD
  • Anaerobic/resistance training has a protective affect against NAFLD

• Aerobic vs. Aerobic + resistance training
  • Both improve NAFLD, but combo exercise better

Zelber-Saqi et al Hepatology 2008, Barritt, AGA Perspectives, 2013
Exercise is good for you...

Moderate to Vigorous Physical Activity Volume is an Important Factor for Managing Non-alcoholic Fatty Liver Disease: A Retrospective Study

- Prevalence of NAFLD among middle aged men in Japan >40%
- 169 obese middle aged men with non-cirrhotic NAFLD, 12 week exercise regimen
  - 3 groups of moderate exercise 2.5-4 hrs/week
  - 1680 kcal dietary restriction

**Hepatic stiffness**

<table>
<thead>
<tr>
<th></th>
<th>I_{m250}</th>
<th>II_{m250}</th>
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<tbody>
<tr>
<td>kpa</td>
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<td>5.45</td>
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<td>6.79</td>
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**Hepatic steatosis**

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<th>II_{m250}</th>
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<tr>
<td>dB/m</td>
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<td>213.9</td>
</tr>
<tr>
<td></td>
<td>286.2</td>
<td>195.1</td>
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</table>

Oh et al, Hepatology 2015
Coffee?

- >2.25 billion cups of coffee consumed worldwide daily
- Coffee has been credited in improving many liver diseases
  - HCC, ETOH, HCV
  - NAFLD
    - Reduces intrahepatic fat via lysosomal autophagy

How much is enough?

- Those who drink 2+ cups daily have ½ rate of chronic liver disease compared to those who drink <1 cup daily
- 38% lower risk of HCC (any vs. none)

Association of Coffee Consumption with Fatty Liver Disease, NASH and Degree of Fibrosis

• Caffeine consumption is associated with reduced fibrosis in HCV
• Case control study using prior U/S based NAFLD prevalence data
  – Used a validated questionnaire for caffeine consumption
  – **177 controls vs. 129 w/ steatosis on U/S**
    • 89 simple steatosis
    • 31 NASH stage 0-1 fibrosis
    • 9 NASH stage 2-4 fibrosis
  – Inverse association btw caffeine/coffee consumption and degree of fibrosis
  – **Logistic regression model showed only 10% risk of advanced fibrosis among those who consumed >2.5 cups of coffee/day**

Molloy, et al, AASLD 2010
WHERE WE ARE TODAY

Alcohol, 2016 AASLD abstracts, East vs. West
Alcohol

• By its definition a NAFLD diagnosis requires the absence of significant ETOH intake
  – Arbitrarily defined at <20g/day

• There is a real world overlap in alcohol consumption and NAFLD risk factors
  – Histology of ASH and NASH is difficult to distinguish

• Many Hepatologists are concerned about the additive effects of ETOH consumption with diabetes and obesity
  – Part of 2 hit hypothesis pushing steatosis toward steatohepatitis
Different perspective...

- Patients with NAFLD die of cardiovascular disease
- Moderate alcohol use may be beneficial for cardiac risk factors and cardiac mortality
- Could patients with NAFLD benefit from moderate alcohol use?
Multiple studies of Japanese men have shown a protective effect of light to moderate ETOH consumption and risk of fatty liver. 1552 daily drinkers compared to 1104 non drinkers – ETOH associated with less fatty liver until 80g/day threshold. Follow up longitudinal study showed remission of prevalent fatty liver among daily drinkers and people who drink 4-6 days/week. Specific dietary and ETOH details not available. Many studies in this area from Asian populations. Generalizability to US and NC? Biased sample?
AASLD 2016
Caution with applying abstract data into clinical practice...

Alcohol good
• Low to moderate lifetime alcohol consumption is associated with less advanced stages of fibrosis in nonalcoholic fatty liver disease
  – Prospective study of 120 Swedish patients
  – ETOH consumption up to 13 units per week associated with lower fibrosis stage

Alcohol bad
• No Benefit from Modest Alcohol Use in Nonalcoholic Fatty Liver Disease (NAFLD)
  – 304 participants from NASH CRN with paired liver biopsies
    • 187 ≤ 2 drinks/day
    • 117 abstinent
  – Moderate drinkers had less improvement in steatosis and no difference in other markers

Hagstrom et al, AASLD 2016, Abs# 36
Ajmera et al, AASLD 2016, Abs# 31
Type of alcohol +/- dietary habits

- French supermarket study of ~200,000 patrons
  - Examined relationship btw alcohol and food choices
  - Identified marked differences in types of alcohol purchases and food choices
  - Revealed a critical unidentified confounding feature in analyses of the potential relationship between alcohol consumption and protection against cardiovascular disease

Proportion of annual grocery budget spent on “healthy” foods

**Healthy Foods:**
- tea, coffee, margarines, fish, vegetable, fruits, low-fat dairy products, vegetables, white meat, and vegetable oils

**Unhealthy Foods:**
- sugar, cheese, salt, high-fat dairy products, factory-made processed products, cakes, soft drinks, biscuits, and butter.

What you eat or when you eat?

- Not Just What, but also When You Eat: Analyzing the Impact of Meal Timing Patterns on Non-Alcoholic Fatty Liver Disease
  - Hepatic metabolic pathways exhibit circadian rhythmicity
  - Data was obtained from NHANES III
- 9015 patients included in the analysis.
  - More meals per day lowered the odds of severe steatosis and high NFS by about 10%.
  - Consuming a greater % of the day’s calories in the morning decreased the odds of steatosis by up to 14-21%.
  - Skipping morning and midday meals were associated with a 20% and 73% rise in steatosis odds, respectively.

Your grandmother is correct, breakfast is the most important meal of the day!

Esteban et al, AASLD 2016, Abs 34
Traditional Chinese Medicine (TCM) in NASH

• Many patients want to take (or may be already taking and not telling you) herbal, alternative, complementary, or TCM to treat medical problems

• Data on clinical efficacy and safety are sparse

• Rising source of DILI
  – Problems with ingredients, drug concentrations, and adulterants
TCM in NASH

A Review of Western and Traditional Chinese Medical Approaches to Managing Nonalcoholic Fatty Liver Disease

Wei-Fan Hsu,¹ Lee-Yan Sheen,² Hung-Jen Lin,³,⁴ and Hen-Hong Chang³,⁴,⁵

• Authors reviewed guidelines from AASLD, EASL and APASL for management of NASH

• Review of ~15 TCM and data supporting use
  – all data at cellular or small animal level

Hsu et al, Evidence based CAM, 2016
TCM proposed mechanisms of action

- TCM are proposed to target similar pathways as Western medicines
  - PPAR
  - Insulin sensitivity
  - Oxidative stress
  - Hepatic fat

- Many products are readily available (e.g. curcumin) and have already come onto the market place for other uses
- Providers should make patients aware of lack of human data

Hsu et al, Evidence based CAM, 2016
Clinical trials for new NASH therapies, transplant

WHERE WE ARE GOING
Mechanisms of action in NASH therapy

**Farnesoid X Receptor**

- FXR agonist will decrease hepatic fat and may improve insulin resistance
- Significance on LDL unknown

**Peroxisome Proliferator-Activated Receptor**

- PPAR agonists improve insulin resistance, lipid metabolism and glucose homeostasis
- Anti-inflammatory
Molecular Mechanisms of Hepatic Steatosis

De novo lipogenesis

FXR agonist (obeticholic acid)

GLP-1 analogue (Liraglutide)

Reduced FA oxidation

Hepatic TG accumulation

Increased FA uptake (obesity)

Reduced VLDL secretion

Adapted from Clinical and Molecular Hepatology 2013: 19; 210
Histologic Changes of NASH

- NAS Components
- A score of 1–3 represents simple steatosis and 4–8 NASH

<table>
<thead>
<tr>
<th>Item</th>
<th>Score</th>
<th>Extent</th>
</tr>
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<tbody>
<tr>
<td>Steatosis</td>
<td>0</td>
<td>&lt;5%</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>5-33%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>&gt;33-66%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>&gt;66%</td>
</tr>
<tr>
<td>Lobular Inflammation</td>
<td>0</td>
<td>No foci</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>&lt;2 foci/200x</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2-4 foci/200x</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>&gt;4 foci/200x</td>
</tr>
<tr>
<td>Hepatocyte Ballooning</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Few balloon cells</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Many cells/prominent ballooning</td>
</tr>
</tbody>
</table>

Hepatology 2005; 41: 1313–21; CMAJ 2005;172:899-905
FLINT trial

Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial

Brent A Neuschwander-Tetri, Rohit Loomba, Arun J Sanyal, Joel E Lavine, Mark L Van Natta, Manal F Abdelmalek, Naga Chalasani, Srinivasan Dasarathy, Anna Mae Diehl, Bilal Hameed, Kris V Kowdley, Arthur McCullough, Norah Terrault, Jeannie M Clark, James Tonascia, Elizabeth M Brunt, David E Kleiner, Edward Doo, for the NASH Clinical Research Network*

• Background: The bile acid derivative 6-ethylchenodeoxycholic acid (obeticholic acid) is a potent activator of the farnesoid X nuclear receptor
  – FXR activation decreases hepatic lipogenesis and decreases cholesterol conversion to bile acids

• Assessed the efficacy of obeticholic acid in non-cirrhotic adult patients with non-alcoholic steatohepatitis.

Neuschwander-Tetri et al, Lancet 2015; 385:956
FLINT trial- results

• 141:142 obeticholic acid 25mg qd vs. placebo for 72 wks.
• 45% improved liver histology compared with 21% in the placebo group
  — (relative risk 1·9, 95% CI 1·3 to 2·8; p=0·0002).
• 23% in the obeticholic acid developed pruritus compared with 6% in the placebo group.
• OCA patients had inc. TC and LDL with dec. HDL

Neuschwander-Tetri et al, Lancet 2015; 385:956
FLINT trial

• Large Phase 3 clinical trial required to determine efficacy and safety (REGERNERATE)
  – Less than 50% of patients on OCA had benefit (subset?)
  – Will pruritus be limiting?
  – Will CV risk with increased LDL be an issue?

Neuschwander-Tetri et al, Lancet 2015; 385:956
Elafibranor (GOLDEN trial)

Elafibranor, an Agonist of the Peroxisome Proliferator — Activated Receptor — $\alpha$ and $\delta$, Induces Resolution of Nonalcoholic Steatohepatitis Without Fibrosis Worsening

- Elafibranor is a PPAR agonist which improves insulin sensitivity, glucose homeostasis, lipid metabolism and reduces inflammation
- Phase II clinical trial of patients with NASH
  - Elafibranor 80mg  n=93
  - Elafibranor 120mg  n=91
  - Placebo n=90
- Study x 52 weeks, 1* outcome of resolution of NASH without fibrosis worsening
Elafibranor

• Results
  – ITT: no difference between drug and placebo
  – NASH resolved without fibrosis worsening in a higher proportion of patients in the 120-mg elafibranor group vs the placebo group (19% vs 12%; based on a post-hoc analysis for modified NASH definition.)
  – In post-hoc analyses of patients with at least NAS 4, elafibranor 120 mg resolved NASH in larger proportions of patients than placebo based on the protocol definition (20% vs 11)
  – Patients with NASH resolution after receiving elafibranor 120 mg had reduced liver fibrosis stages compared to those without NASH resolution
  – Drug well tolerated
  – Secondary end points all showed improvement in elements of the metabolic syndrome

Ratziu, Gastro 2016
Elafibranor

• Results

<table>
<thead>
<tr>
<th>Population</th>
<th>Selection, n</th>
<th>Placebo</th>
<th>Elafibranor 80 mg</th>
<th>Elafibranor 120 mg</th>
<th>OR (95% CI)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>All NAS ≥4</td>
<td>234&lt;sup&gt;b&lt;/sup&gt;</td>
<td>76 (9)</td>
<td>83 (13)</td>
<td>75 (19)</td>
<td>3.52 (1.32–9.40)</td>
<td>.013</td>
</tr>
<tr>
<td></td>
<td>202&lt;sup&gt;c&lt;/sup&gt;</td>
<td>63 (11)</td>
<td>72 (15)</td>
<td>67 (21)</td>
<td>3.26 (1.17–9.02)</td>
<td>.024</td>
</tr>
<tr>
<td>NAS ≥4 with fibrosis (any stage)</td>
<td>204&lt;sup&gt;b&lt;/sup&gt;</td>
<td>66 (11)</td>
<td>67 (15)</td>
<td>71 (20)</td>
<td>3.75 (1.39–10.12)</td>
<td>.009</td>
</tr>
<tr>
<td></td>
<td>176&lt;sup&gt;c&lt;/sup&gt;</td>
<td>55 (13)</td>
<td>58 (17)</td>
<td>63 (22)</td>
<td>3.22 (1.15–8.99)</td>
<td>.026</td>
</tr>
<tr>
<td>NAS ≥4 with moderate/advanced</td>
<td>118&lt;sup&gt;b&lt;/sup&gt;</td>
<td>41 (7)</td>
<td>39 (10)</td>
<td>38 (13)</td>
<td>18.46 (4.80–70.96)</td>
<td>.0001</td>
</tr>
<tr>
<td>fibrosis (F2, F3)</td>
<td>99&lt;sup&gt;c&lt;/sup&gt;</td>
<td>32 (9)</td>
<td>33 (12)</td>
<td>34 (15)</td>
<td>10.59 (2.52–44.50)</td>
<td>.002</td>
</tr>
</tbody>
</table>

<sup>a</sup>120 mg elafibranor vs placebo, direct treatment effect.

• Modified end points were sufficient to justify phase III clinical trial (RESOLVE-IT)

Ratziu, Gastro 2016
Liraglutide (LEAN trial)

Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study

- Liraglutide is a glucagon-like peptide-1 (GLP-1) analogue approved to treat DM which reduces hepatic steatosis, liver enzymes, and insulin resistance.
- Phase II clinical trial of patients with NASH
  - Liraglutide 1.8mg sq weekly n=26
  - Placebo n=26
- Study x 48 weeks, 1* outcome of resolution of NASH without fibrosis worsening

Armstrong, Lancet 2016; 387:679
Liraglutide (LEAN trial)

Results:

Weight loss and decreased ALT also seen with drug

Caveats: Very small study, low placebo response, cirrhosis already present in 8% study grp and 15% placebo grp

Armstrong, Lancet 2016; 387:679
Phase I and II

Multiple companies actively working on investigational products for NASH

- BMS
- NuSirt
- Gilead
- Cempra
- Tobira
- Conatus
- Madrigal
- Can-Fite
- Galactin
- Nimbus
Challenge will continue

• If/when there are successful FDA approved interventions for NASH, questions and challenges will remain
  – Are these lifetime drugs?
  – Interventions to pause disease while patients fix lifestyle problems
  – CV risk
  – Cancer risk
  – Trial efficacy vs. real world effectiveness
NASH Target

• Real world observational trial
  – Similar in structure and design to HCV Target
  – Any patient with a clinical or biopsy proven diagnosis of NAFLD
  – Includes patients with cirrhosis
  – Goal is to describe real world practice and natural history of disease with ability to perform phase 4 surveillance of new drugs once released.
Liver Transplantation

- NAFLD and NASH will impact both the donor and recipient transplant population
- We examined waitlist trends by region and disease etiology and then simulated the waitlist characteristics over the next decade
- The liver transplant waitlist size will remain relatively static on a national level over the next decade. This balance will not be achieved by additional transplants but by waitlist dropout instead.

Yi et al AASLD 2016 abs # 1400, 1403
Liver Transplantation

- Over the next decade, NASH will become the leading disease etiology for liver transplantation
- Patents will be older and wait longer for transplant
- Risk of waitlist drop out will increase

<table>
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<tr>
<th></th>
<th>Year</th>
<th>Male (%)</th>
<th>Age&gt;=60 (%)</th>
<th>HCV (%)</th>
<th>NASH (%)</th>
<th>HCC (%)</th>
<th>Expected Wait time for MELD 22-27, days</th>
<th>waitlist drop out (%)</th>
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<td><strong>Baseline Scenario</strong></td>
<td>2015</td>
<td>64.7</td>
<td>35.9</td>
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<td>18.2</td>
<td>16.5</td>
<td>82</td>
<td>41.3</td>
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<td>2020</td>
<td>64.5</td>
<td>44.9</td>
<td>22.9</td>
<td>21.1</td>
<td>25.5</td>
<td>123</td>
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<td>28.5</td>
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<td>45.8</td>
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<td>35.3</td>
<td>30.2</td>
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<td>15.4</td>
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<td>47.7</td>
<td>19.6</td>
<td>20.7</td>
<td>32.4</td>
<td>368</td>
<td>69.9</td>
</tr>
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</table>

Yi et al AASLD 2016 abs # 1400, 1403
Overview

1. Diet and exercise remain the backbone of NASH therapy
   – Reduced calorie diet may be more important than content
   – Don’t skip meals (and then binge eat)

2. Pharmacologic interventions on the horizon but not ready yet
   – OCA and elafibranor closest to market
   – Moot unless we can fix #1?
   – Little data to support TCM or herbals at this point
     • I discourage their use

3. Successful NASH therapy will take a multidisciplinary approach with a long term outlook for a chronic disease
   – Nutritionists, psychologists, medical providers

4. NASH will need to be addressed aggressively in the pre-cirrhotic stage as transplant may not be a long term solution for this population
UNC Comprehensive NAFLD Clinic

• Hepatology Care
  – Diagnostic evaluation
  – Non invasive assessment of disease
  – Liver biopsy
  – Endoscopic procedures
  – General cirrhosis care
  – Management of end stage liver disease
  – Transplant Evaluation

• Clinical trials
  – OCA
  – Elafibranor
  – NASH Target
  – Several others coming soon! (need IRB approval before I can advertize them)

• Psychological Services
  – Health Literacy Assessment
  – Adherence Education
  – Assessment of comorbid depression and anxiety
  – Eating disorder management/education

• Nutrition Services
  – Dietician Assessment
  – Diabetic Diet Education
  – Low sodium diet education
  – Fluid restriction diet education