Recent Advances in the Management of NAFLD

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December 7, 2019
This presentation focuses on the following three topics:

1. Update on the pathogenesis and natural history of NAFLD
2. Update on strategies for risk stratification of NAFLD
3. Update on management of NAFLD
Liver fibrosis is the most important prognostic factor for clinical outcomes in NAFLD

Image source: The AURORA study, Tobira Therapeutics
High-risk genetic polymorphisms are associated with the prevalence of NAFLD

- GCKR rs1260326
- TM6SF2 rs58542926
- TMC4- MBOAT7 rs641738,
- PNPLA3 rs738409
- HSD17B13 rs72613567
- HSD17B13 rs80182459

Kubilian et al, Liver Meeting 2019
Liver-related as well as non-liver related complications increase with advancing fibrosis.
Cardiovascular disease and extra-hepatic cancers are common causes of death in patients with NAFLD

![Bar chart showing intimal medial thickness in healthy controls, simple steatosis, and NASH patients.](chart1)

A. Intimal Medial Thickness (mm)
- Healthy Controls (N=160)
- Simple Steatosis (N=16)
- NASH (N=69)

B. Intimal Medial Thickness (mm)
- Stage 0 (N=23)
- Stage 1 (N=25)
- Stage 2 (N=13)
- Stage 3 (N=8)

Fibrosis Stage in NASH

*P < 0.001 for all comparisons*

Targer, 2010, NEJM
The NAFLD Simulator is a helpful tool to facilitate conversations with patients about risk stratification.
Vibration Controlled Transient Elastography (Fibroscan®) is very useful for point-of-care risk stratification.

Steatosis cutoff: 274 dB/m for grade ≥1 steatosis [sensitivity of .90 (95% CI .87-.93)]

Fibrosis: liver stiffness measurement cutoff values of 8.2 kPa for ≥F2, 9.7 kPa for ≥F3 and 13.6 kPa for F4.
Ultrasound Shear Wave Elastography is equivalent to VCTE/Fibroscan for noninvasive fibrosis assessment.
MR Elastography and proton density fat fraction (PDFF) can accurately measure liver fibrosis and steatosis

Furlan, 2019, Am J Roent.
Noninvasive approaches to fibrosis assessment can avoid liver biopsy in a large percentage of patients.

35 year old male
NAFLD Fibrosis Score: -2.15

Furlan, 2019, Am J Roent.
Several new technologies are on the horizon for imaging-based assessment of liver fat and fibrosis

Multiparametric three-dimensional magnetic resonance elastography (3D-MRE)

<table>
<thead>
<tr>
<th>Baseline before treatment</th>
<th>1 year after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stiffness (kPa)</td>
<td>Stiffness (kPa)</td>
</tr>
<tr>
<td>Shear Stiffness = 4.37 kPa</td>
<td>Shear Stiffness = 2.63 kPa</td>
</tr>
<tr>
<td>Damping Ratio = 0.11</td>
<td>Damping Ratio = 0.15</td>
</tr>
<tr>
<td>PDFF = 25.9 %</td>
<td>PDFF = 3.9 %</td>
</tr>
</tbody>
</table>

Predicted NAS:  | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
Histologic NAS: 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |

Probability of NASH: 0.99
Histologic Diagnosis: NASH

Predicted NAS:  | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
Histologic NAS: 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |

Probability of NASH: 0.35
Histologic Diagnosis: Not NASH

Allen et al, 2019, Hepatol Comm
Imaging-based technologies will allow rapid noninvasive assessment of liver fat and inflammation

Multiparametric magnetic resonance imaging (Liver Multiscan)

57 yo overweight female with 6 months of lifestyle intervention

MONTH 0

PDFF: 16.5%
Normal range: <5.6%

T2*: 14.5ms
Normal range: >12.5ms

cT1: 878.4ms
Reference interval: 633ms – 794ms

MONTH 6

PDFF: 2.4%
Normal range: <5.6%

T2*: 16.2ms
Normal range: >12.5ms

cT1: 738.3ms
Reference interval: 633ms – 794ms

Image source: Perspectum Diagnostics
Consider a systematic risk-stratified approach to NAFLD management

M: ALT > 30; F > 19
Repeat labs; Risk factors

Alcohol history, HBsAg, HCV Ab, ferritin/iron sat, ANA, ASMA, AIAT level, ceruloplasmin

Treat as appropriate

Abd US echobright
Liver screen negative

NAFLD Fibrosis score
VCTE/2D-SWE/MRE

Low risk:
NFS < -1.455 (NPV 93%)
VCTE < 7 kPa*

< -2.5
< 5 kPa

-1.45 to -2.5
5-7 kPa

Indeterminate
NFS -1.455-0.676
VCTE 8.2-13.5*
OR Discordant NFS/VCTE

Liver biopsy
Treat if F2-3 fibrosis

High risk
NFS > 0.676 (PPV 90%)
VCTE > 13.5 (+/-1) kPa*

Alternate diagnosis?
Mild steatosis?

PCP follow up/3 years
Reassess in 1 year
Lifestyle mod.

Manage as cirrhosis

* Cutoffs not validated
It is helpful to consider a risk-stratified management strategy for NAFLD

- **Early-stage NAFLD**: Steatosis alone
- **Intermediate**: NASH stage 1–3 fibrosis
- **Late-stage NAFLD**: NASH with cirrhosis

**Lifestyle intervention such as diet and exercise changes**

**Bariatric surgery such as gastric bypass or sleeve gastrectomy**

**Pharmacological therapy**
- Current therapies:
  - Vitamin E
  - Pentoxifylline
  - Insulin sensitizers
- Therapies in development:
  - Obeticholic acid
  - GFT505

**Screening for HCC and oesophageal varices**

* Rinella, 2016
Despite relatively low probability of long-term success, weight loss is an excellent treatment option for NAFLD.
Weight loss surgery is effective in resolving NASH but liver fibrosis may not regress in some patients

82 patients at 1 year after surgery

Despite weight loss >20 kg and NASH resolution, 45% of patients did not achieve resolution of advanced fibrosis (F/4) after 6 years*

Lassailly, 2015, Gastroenterology
*Pais, 2019 Liver Meeting
Vitamin E (with modest weight loss) is effective in improving NASH in NAFLD patients without diabetes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Vitamin E</th>
<th>Pioglitazone</th>
<th>Vitamin E vs. Placebo</th>
<th>Pioglitazone vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects randomly assigned</td>
<td>83</td>
<td>84</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with improvement (%)</td>
<td>19</td>
<td>43</td>
<td>34</td>
<td>0.001</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Changes from baseline in histologic features</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No. of subjects with biopsy specimens at baseline and 96 wk</td>
<td>72</td>
<td>80</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steatosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with improvement (%)</td>
<td>31</td>
<td>54</td>
<td>69</td>
<td>0.005</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean change in score</td>
<td>−0.1</td>
<td>−0.7</td>
<td>−0.8</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lobular inflammation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with improvement (%)</td>
<td>35</td>
<td>54</td>
<td>60</td>
<td>0.02</td>
<td>0.004</td>
</tr>
<tr>
<td>Mean change in score</td>
<td>−0.2</td>
<td>−0.6</td>
<td>−0.7</td>
<td>0.008</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hepatocellular ballooning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with improvement (%)</td>
<td>29</td>
<td>50</td>
<td>44</td>
<td>0.01</td>
<td>0.08</td>
</tr>
<tr>
<td>Mean change in score</td>
<td>−0.2</td>
<td>−0.5</td>
<td>−0.4</td>
<td>0.03</td>
<td>0.01</td>
</tr>
<tr>
<td>Total NAFLD activity score (mean change)</td>
<td>−0.5</td>
<td>−1.9</td>
<td>−1.9</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrosis‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with improvement (%)</td>
<td>31</td>
<td>41</td>
<td>44</td>
<td>0.24</td>
<td>0.12</td>
</tr>
<tr>
<td>Mean change in score</td>
<td>−0.1</td>
<td>−0.3</td>
<td>−0.4</td>
<td>0.19</td>
<td>0.10</td>
</tr>
<tr>
<td>Resolution of definite nonalcoholic steatohepatitis (% of subjects)</td>
<td>21</td>
<td>36</td>
<td>47</td>
<td>0.05</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Pioglitazone is an option to treat NASH with fibrosis in patients with NASH and T2DM or prediabetes

45 mg/d x 18 months
2.5 kg weight gain vs placebo
Several new therapies are in advanced stages of testing and have shown promising results in treating NASH.
Obeticholic acid (OCA) has shown promising results in treatment of NASH and fibrosis but can cause itching.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>OCA 10 mg</th>
<th>OCA 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population with F1-F3 fibrosis</td>
<td>n=407</td>
<td>n=407</td>
<td>n=404</td>
</tr>
<tr>
<td>Fibrosis improvement + no worsening of NASH</td>
<td>10.6%</td>
<td>15.7% p&lt;0.029</td>
<td>21% p&lt;0.0001</td>
</tr>
<tr>
<td>NASH resolution + no worsening of fibrosis</td>
<td>7.9% p=0.09</td>
<td>11.3% p=0.001</td>
<td>14.9%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>19%</td>
<td>28%</td>
<td>51%</td>
</tr>
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</table>

Phase 3 REGENERATE trial: Interim analysis at 18 months based on surrogate endpoints (impact on clinical outcomes not yet established)

Adapted from Sanyal, 2019 Liver Meeting
A multidisciplinary approach is needed to manage NAFLD-associated comorbid metabolic problems

- **Diagnosis of NAFLD**
- **Screen for Metabolic Risk Factors**
  - **Obesity**
    - Body mass index >30
  - **Diabetes Mellitus**
    - Hemoglobin A1c >6.5%, random glucose >200 mg/dL, or fasting glucose >126 mg/dL on 2 separate occasions
  - **Dyslipidemia**
    - 10-year atherosclerotic cardiovascular disease risk score >7.5%, LDL > 190 mg/dL, or LDL > 70-189 mg/dL with diabetes
  - **Hypertension**
    - Blood pressure >140/90 mm Hg on at least 2 separate measurements
- **Management Goals of Metabolic Risk Factors**
  - **Weight loss of 7%-10% over 48%-52 weeks**
  - **Hemoglobin A1c <7.0% with lifestyle modifications +/- antiglycemic agent(s)**
  - **Treat using a moderate- to high-intensity statin. Expect •50% reduction in LDL from baseline using high-intensity statin. Expect 30%-50% reduction in LDL from baseline using moderate-intensity statin.**
  - **Systolic blood pressure <150 or <140 mm Hg depending on age, presence of diabetes, and/or chronic kidney disease; diastolic blood pressure <90 mm Hg**

*Wong and Lim, 2018, Clin Liv Dis*
Metformin may decreasing overall mortality and statin therapy is safe in NAFLD

A

NASH-induced Cirrhosis

\[ P = 0.0004 \]

Survival probability (%)

Time after diagnosis of cirrhosis (Years)

Continued Metformin (n=98)

Discontinued Metformin (n=44)

B

Non-NASH induced Cirrhosis

\[ P = 0.09 \]

Survival probability (%)

Time after diagnosis of cirrhosis (Years)

Continued Metformin (n=74)

Discontinued Metformin (n=34)

Zhang, 2014, Hepatology
In summary, systematic risk stratification with weight loss and pharmacotherapy is recommended for NAFLD.