GET READY FOR THE GLOBAL EPIDEMIC OF NASH EVOLVING DIAGNOSIS AND TREATMENT STRATEGIES

This symposium is not affiliated with UEG.
Supported by an educational grant from Intercept Pharmaceuticals, Inc.
ZOBAIR M. YOUNOSSI, MD, MPH
Chairman, Department of Medicine, Inova Fairfax Medical Campus
Vice President for Research, Inova Health System
Professor of Medicine, Virginia Commonwealth University, Inova Campus
Affiliate Professor of Biomedical Sciences, George Mason University
Falls Church, Virginia, USA

VLAD RATZIU, MD, PhD
Professor of Hepatology
Hospital Pitié-Salpêtrière
Institute of Cardiometabolism and Nutrition
Université Pierre et Marie Curie
Paris, France
<table>
<thead>
<tr>
<th>Time</th>
<th>Presenter</th>
<th>Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>6:45 – 7:00</td>
<td>Registration</td>
<td>Registration/Seating</td>
</tr>
<tr>
<td>7:00 – 7:10</td>
<td>Dr. Younossi</td>
<td>Welcome &amp; Introduction to Epidemiology of NAFLD</td>
</tr>
<tr>
<td>7:10 – 7:30</td>
<td>Dr. Ratziu</td>
<td>Recent Advances in the Diagnosis, Management and Treatment of Patients with NASH</td>
</tr>
<tr>
<td>7:30 – 7:40</td>
<td>Dr. Younossi</td>
<td>Case #1: Fatty Liver &amp; HCC</td>
</tr>
<tr>
<td>7:40 – 7:50</td>
<td>Dr. Ratziu</td>
<td>Case #2: Progression of Liver Disease</td>
</tr>
<tr>
<td>7:50 – 8:00</td>
<td>Drs. Younossi &amp; Ratziu</td>
<td>Panel Discussion/Q&amp;A</td>
</tr>
</tbody>
</table>
In accordance with the ACCME Standards for Commercial Support of CME, the speakers for this course have been asked to disclose to participants the existence of any financial interest and/or relationship(s) (e.g., paid speaker, employee, paid consultant on a board and/or committee for a commercial company) that would potentially affect the objectivity of his/her presentation or whose products or services may be mentioned during their presentation. The following disclosures were made:

Faculty
Vlad Ratziu
- **Advisory Board Membership:** Intercept, Genfit, Galmed, Tobira

Zobair Younossi
- **Consultant/Speaker Bureau:** Gilead, Intercept, BMS, GSK, Tobira

Planning Committee Members
John Bayliss, VP, Business Development, Annenberg Center, Spouse - Employee of Amgen, Inc
Lisa D. Pedicone, PhD, Medical Writer, Chronic Liver Disease Foundation - No Relevant Relationships

All other Chronic Liver Disease Foundation and Annenberg Center staff have no relevant relationships to disclose.
The Chronic Liver Disease Foundation would like to thank

*Intercept Pharmaceuticals, Inc.*

for providing an educational grant to support this program.
Educational Objectives

Upon completion of this educational activity, participants should be able to:

• Discuss epidemiology and diagnosis of NASH
• Recognize the limitations of current treatment strategies and understand emerging therapeutic approaches
• Develop evidence-based treatment strategies using the latest clinical data
Epidemiology of NAFLD

Zobair Younossi MD, MPH, FACG, AGAF, FAASLD

Chairman, Department of Medicine, Inova Fairfax Hospital
Vice President for Research, Inova Health System
Professor of Medicine, VCU-Inova Campus
Affiliate Professor of Biomedical Sciences,
George Mason University
Falls Church, Virginia
Epidemiology and Clinical Outcomes of NAFLD

NAFLD is a Phenotype that Includes a Histopathologic Spectrum with Diverse Pathogenic Mechanisms and Differential Risks for Progression

- NASH requires specific pathologic criteria
- Exclusion of liver diseases
- Important for prognosis

The Global Prevalence of NAFLD

- Pubmed and MEDLINE databases were searched from 1989-2015 for terms involving epidemiology and progression of NAFLD.
- Out of 729 studies, 86 were included with a sample size of 8,515,431 from 22 countries.
- Global prevalence of NAFLD is 25.24% (22.10-28.65) with highest prevalence in Middle East and South America and lowest in Africa.

Economic Burden of Non-alcoholic Fatty Liver Disease

- 5 economic models for NAFLD (USA and GR, FR, IT & UK)
- Models were built using interlinked Markov chains
- NAFLD (9 transition health states: NAFL, NASH, NASH-fibrosis, NASH-CC, NASH-DCC, HCC, LT, pLT and death)
  - Incidence/remission rates calibrated against real-world rates.
  - The data was validated using DisMod II
  - Utilities from NAFLD patients and costs from literature & fee schedules
- In the US, over 64 million people with NAFLD, with annual direct medical costs of about $103 bn [$1,613 PP].
- In EU-4 countries ~52 million people with NAFLD with an annual cost of about € 35 billion (€ 354 to € 1,163 PP)
  - Costs are highest in patients aged 45-65.
  - Burden is higher when societal costs are included.

NAFLD and Long Term Outcomes: Mortality

- Histologic NAFLD (N=289)
  - NASH (59.2%), non-NASH (40.8%)
  - NASH patients were predominantly female, had higher AST, ALT and higher fasting serum glucose
- Mortality: Median follow-up of 150 months
  - NASH patients had higher risk of liver-related mortality than non-NASH NAFLD (p-value = 0.0026).

Predictors of Mortality

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Overall mortality aHR (95% CI)</th>
<th>Liver mortality aHR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASH</td>
<td>1.13 (0.74 - 1.71)</td>
<td>9.16 (2.10 - 9.88)</td>
</tr>
<tr>
<td>Age</td>
<td>1.07 (1.05 - 1.10)</td>
<td>1.06 (1.02 - 1.10)</td>
</tr>
<tr>
<td>Male</td>
<td>0.95 (0.62 - 1.47)</td>
<td>1.44 (0.62 - 3.34)</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.91 (0.60 - 1.40)</td>
<td>0.88 (0.38 - 2.04)</td>
</tr>
<tr>
<td>DM</td>
<td>2.09 (1.39 - 3.14)</td>
<td>2.19 (1.00 - 4.81)</td>
</tr>
</tbody>
</table>

NAFLD and Long Term Outcomes: HCC and OLT

- HCC (N=4,979) (SEER 2004–2009) & 14,937 non-HCC
- Number of HCC cases increased between 2004-2009

**Causes of CLD in HCC**

- NAFLD 14%
- HBV 9%
- Autoimmune hepatitis/biliary cirrhosis 5%
- Alcoholic 16%
- HCV 56%

**MORTALITY:** With 1-yr of Diagnosis, fewer HCV/HBV than NAFLD (53% vs. 61%, p<0.05)

**Adjusted Survival Curve by Liver Disease**

Age, ESRD, advanced HCC, CCI, ALD (HR 1.27 (1.06-1.54) & NAFLD 1.21 (1.01-1.45) independently associated with mortality within 1-yr

- OPTN (2004-2013) LT list
  - New waitlist for NASH increased by 170%
  - ALD increased by 45%
  - HCV increased by 14%
- NASH has become the 2nd indication for LT listing (2013)

- 90 day on the list mortality:
  - ALD lower than NASH: OR: 0.77; 0.67–0.89; P < .001
  - NASH similar to HCV
- Compared to HCV, NASH patients had the lowest chance of getting transplanted in 90 days and 1 year

What Are the Histologic Predictors of Mortality In NAFLD?

- NAFLD liver biopsy and mortality data (N=209)
- Biopsies were read centrally
- During follow-up (146 months), 31% of patients died with 9% dying of LRM
- Despite the pathologic protocol, NASH had higher LRM than non-NASH NAFLD
  - 13.0% vs. 1.3%, p = 0.0047

<table>
<thead>
<tr>
<th>Univariate survival analyses [HR (95% CI), p-value]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portal inflam (grade≥2)</td>
</tr>
<tr>
<td>Ballooning (grade≥2)</td>
</tr>
<tr>
<td>MD bodies (grade≥2)</td>
</tr>
<tr>
<td>Portal fib (grade&gt;2)</td>
</tr>
<tr>
<td>Pericellular fib (grade&gt;2)</td>
</tr>
</tbody>
</table>

On multivariate analysis, only significant fibrosis (grade > 2) was an independent predictor of LRM

<table>
<thead>
<tr>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis Stage</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>

Progressiveness

Cirrhosis

Stable

NAFL

Stable

NAFLD

10-15%

NASH

65-75%

Liver Failure

20-30%

Death

HCC

(Annual incidence 2%)

Cirrhosis

40-60%

Summary

- About one fourth of world’s population have NAFLD
- The subgroup of NASH is progressive
- In the US, NASH is the second leading indication for LT and HCC
- The economic burden of NAFLD is enormous and increasing
Recent Advances in the Diagnosis, Management and Treatment of Patients with NASH

Vlad Ratziu, MD, PhD

Université Pierre et Marie Curie, Hôpital Pitié Salpêtrière, Paris, France
NAFLD

Secondary

- Alcohol
- Drugs (amiodarone, metothrexate, tamoxifen, corticosteroids)
- A/hypo betalipoprotéinémia
- Chronic HCV (genotype 3)
- Wilson disease
- Industrial toxins
- Lipodystrophies
- Cholesteryl ester storage disease
- Microvesicular steatosis

Primary

Metabolic Risk Factors

- Body Mass index > 25 kg/m² and/or
- Waist circumference > 94 cm in men, 80 cm in women (Caucasians)
- Arterial hypertension > 135/85 mmHg
- Fasting serum glucose > 6.1 mmol/L
- Serum triglycerides > 1.7 mmol/L
- HDL-cholesterol < 1 mmol/L (men); < 1.3 mmol/L (women)
- Serum ferritin > 350 µg/L
- First degree relatives of individuals with obesity and/or diabetes
NAFLD: An Under-recognized Disease

39.4%  Recognition of ALT increase
21.5%  Diagnosis of NAFLD/NASH
15%    Lifestyle modifications
10.5%  Referral specialist evaluation

60.6%  NO NAFLD CARE

Only the magnitude and proportion of ALT elevation were predictive of receiving NAFLD care

**Fibrosis Serum Markers**

**FREE OF CHARGE**

**COMMERCIAL**

**NFS (NAFLD Fibrosis Score)**
Age, glucose, BMI, Plt, Alb, AST/ALT

**FIB4**
Age, ALT, AST, Plt

**Hepascore**
Age, sex, α2macrog, Hyal ac, GGT, Bili

**BARD**
(BMI, AST/ALT, DM)

**APRI**
AST/Plt
Prognostic Value of Non-invasive Markers in NAFLD

MRE Elastography

Stage 0
1.69 kPa

Stage 1
2.11 kPa

Stage 2
3.20 kPa

Stage 3
6.22 kPa

Stage 4
6.91 kPa

MRE Elastography

**A**

**MR Elastography**

Kruskal-Wallis Test

\[ P < .001 \]

<table>
<thead>
<tr>
<th>Fibrosis stage</th>
<th>Cut-off level, kPa</th>
<th>AUROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \geq 1 )</td>
<td>2.5</td>
<td>0.80</td>
</tr>
<tr>
<td>( \geq 2 )</td>
<td>3.4</td>
<td>0.89</td>
</tr>
<tr>
<td>( \geq 3 )</td>
<td>4.8</td>
<td>0.89</td>
</tr>
<tr>
<td>( \geq 4 )</td>
<td>6.7</td>
<td>0.97</td>
</tr>
</tbody>
</table>

**Transient Elastography**

Kruskal-Wallis Test

\[ P < .001 \]

<table>
<thead>
<tr>
<th>Fibrosis stage</th>
<th>Cut-off level, kPa</th>
<th>AUROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \geq 1 )</td>
<td>7.0</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>11.0</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>11.4</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>14.0</td>
<td>0.92</td>
</tr>
</tbody>
</table>

MRE > TE for F\( \geq 2 \) and for cirrhosis

NAFL

NASH no/mild fibrosis

High risk of progression

Significant (F2)

Advanced (F3)

HCC

Cirrhosis
First Records of Chronic Liver Diseases in Scotland by Diabetes Status

- Retrospective population-based cohort
- Scottish Diabetes Register & National hospital cancer and death records
- 2004-2013; 40-89 years; 26 M Pt/years of F/u
- 97% mono diagnosis of CLD

<table>
<thead>
<tr>
<th>Type of liver disease</th>
<th>Type 2 diabetes</th>
<th>No diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deaths</td>
<td>Hospital admissions</td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
<td>213</td>
<td>1773</td>
</tr>
<tr>
<td>Autoimmune liver disease</td>
<td>19</td>
<td>218</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>11</td>
<td>410</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>52</td>
<td>844</td>
</tr>
<tr>
<td>Non-alcoholic fatty liver disease</td>
<td>327</td>
<td>2942</td>
</tr>
<tr>
<td>Viral liver disease</td>
<td>26</td>
<td>220</td>
</tr>
</tbody>
</table>

## Sex-specific Rate Ratios in Diabetes for Chronic Liver Diseases

<table>
<thead>
<tr>
<th>Type of liver disease</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age and SES quintile adjusted</td>
<td>Age and SES quintile adjusted</td>
</tr>
<tr>
<td>Alcoholic liver disease*</td>
<td>1.38 (1.15-1.65)</td>
<td>1.57 (1.28-1.93)</td>
</tr>
<tr>
<td>Autoimmune liver disease</td>
<td>1.50 (1.12-2.01)</td>
<td>1.25 (1.04-1.49)</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>1.67 (1.43-1.94)</td>
<td>1.60 (1.23-1.97)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>3.36 (2.97-3.81)</td>
<td>3.55 (3.02-4.17)</td>
</tr>
<tr>
<td>Non-alcoholic fatty liver disease</td>
<td>3.03 (2.68-3.43)</td>
<td>5.11 (4.45-5.87)</td>
</tr>
<tr>
<td>Viral liver disease</td>
<td>1.38 (0.86-1.92)</td>
<td>2.20 (1.52-3.18)</td>
</tr>
</tbody>
</table>

Work-up in Patients with NAFLD: A Multi-organ Approach

NAFLD

Extrahepatic comorbidities

• Type 2 diabetes
• Sleep apnea
• Arterial hypertension
• Dyslipidemia

Liver condition

• Cofactors of fibrosis
• Pathological form
• Stage
• Prognosis
NAFLD – Center Stage of the Metabolic Syndrome?

- Hypertension
  - Prevalence essential HTN

- Cardiovascular
  - Endothelial & coronary dysfunction
  - Carotid plaques
  - Impaired ventricular fct and metabolism
  - CV events

- Diabetes
  - Incident diabetes
  - Insulin requirements

Incident diabetes
Insulin requirements
Metabolic and Inflammatory Cross Talk
Adipose Tissue – Fatty Liver

- Hyperinsulinemia
- Dysfunctional Adipose Tissue
  - Insulin Resistance
  - Inflammatory signals
    - Lipolysis
    - Lipotoxicity
  - Steatosis / NASH
    - Hyperinsulinemia
      - VLDL production
      - Hepatic lipogenesis
      - CV disease
      - Carcinogenesis
**Fat Distribution and Cardiometabolic Risk**

**TABLE 2.** The association between metabolic health, obesity, and CVD mortality

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases/n</th>
<th>Age- and sex-adjusted HR (95% CI)</th>
<th>Fully adjusted HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole sample</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolically healthy nonobese</td>
<td>225/12716</td>
<td>1.00 (referent)</td>
<td>1.00</td>
</tr>
<tr>
<td>Metabolically unhealthy nonobese</td>
<td>216/4201</td>
<td>1.66 (1.37–2.00)</td>
<td>1.59 (1.30–1.94)</td>
</tr>
<tr>
<td>Metabolically healthy obese</td>
<td>18/1160</td>
<td>1.02 (0.63–1.65)</td>
<td>1.26 (0.74–2.13)</td>
</tr>
<tr>
<td>Metabolically unhealthy obese</td>
<td>145/4128</td>
<td>1.58 (1.28–1.95)</td>
<td>1.64 (1.17–2.30)</td>
</tr>
</tbody>
</table>

*P trend*<0.001

Dysfunctional adipose tissue:

- Increased fasting and post prandial serum insulin
- Impaired insulin suppression of lipolysis
- Increased serum FFAs
- Macrophage infiltration; M1 polarization
- Induction of pro-inflammatory cytokines
- Reduction in adiponectin
- Systemic insulin resistance

**AT-IR index : FFA x Insulin**
Weight Loss Pyramid

- Weight Loss ≥10%¹
- Weight Loss ≥7%¹
- Weight Loss ≥5%¹-³
- Weight Loss ≥3%¹-⁴

- Steatosis (35–100%)*
- Ballooning / inflammation (41–100%)*
- NASH Resolution (64–90%)*
- Fibrosis (45%)

*Depending on degree of weight loss
Slide courtesy of S. Harrison
Weight Loss Pyramid

Patients achieving:
- Fibrosis (45%)
  - <10% in 1 year

- NASH Resolution (64–90%)*
  - 18% in 1 year

- Ballooning / inflammation (41–100%)*
  - 30% in 1 year

- Steatosis (35–100%)*

*Depending on degree of weight loss
Slide courtesy of S. Harrison
Predictors of NASH Resolution After 52 Weeks of Diet/Lifestyle Changes

- ALT normalization
- Weight loss
- Type 2 diabetes *(negative)*
- Age ≥46 yrs *(negative)*
- NAS≥5 *(negative)*

Who Should be Treated?

NAFL

NASH no/mild fibrosis

High risk of progression

Significant (F2)

Advanced (F3)

HCC

Cirrhosis

??
Obeticholic Acid

- **OCA** (6a-ethyl chenodeoxycholic acid)
- **CDCA** (chenodeoxycholic acid)
- **UDCA** (ursodeoxycholic acid)

FXR EC\textsubscript{50} (agonist) 0.099 \mu M 8.66 \mu M No activity

\[ \sim 100x \uparrow \text{FXR agonism} \]

**Improvement in insulin sensitivity in clamp studies in diabetic patients**

Primary endpoint: Histological improvement defined as:
- No worsening in fibrosis; and
- Decrease in NAS of ≥ 2 points
Primary Outcome: Improved Liver Histology After 72 Weeks of Treatment

Patients Achieving the Primary Outcome Measure:
>2 point improvement in NAFLD activity score without worsening of fibrosis

***p<0.001; Relative risk (95% CI): 1.9 (1.3 to 2.8); p-value and relative benefit were obtained using Cochran-Mantel-Haenszel Chi-square test stratified by center and diabetes status; Missing week 72 biopsy results were imputed as no improvement among patients at risk of week 72 biopsy; Neuschwander-Tetri BA, et al. Lancet. 2014:S0140-6736(14)61933-4.
Secondary Outcomes: Improvement in Histological Parameters

% Patients Achieving Improvement in Histological Features at Week 72

Lobular Inflammation
Steatosis
Hepatocellular Ballooning
Fibrosis

Placebo (n=98)
Obeticholic Acid (n=102)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Placebo (%)</th>
<th>Obeticholic Acid (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobular Inflammation</td>
<td>35</td>
<td>53</td>
</tr>
<tr>
<td>Steatosis</td>
<td>38</td>
<td>61</td>
</tr>
<tr>
<td>Hepatocellular Ballooning</td>
<td>31</td>
<td>46</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>35</td>
<td>19</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01, ***p<0.001; p-value was based on the Cochran-Mantel-Haenszel chi-square test stratified by center and diabetes status; Neuschwander-Tetri BA, et al. Lancet. 2014:S0140-6736(14)61933-4.
Primary Endpoint Analysis in Higher Risk Subgroups

Improvement defined as decrease at least 2 points in the total NAFLD activity score without worsening of fibrosis
*p<0.05, ***p<0.001; p-values are based on the Cochran-Mantel-Haenszel chi-square test stratified by center and diabetes status.
ALT = Alanine Aminotransferase; BMI = body mass index;
Changes from Baseline in Serum Lipid Concentrations

**Total Cholesterol**

**LDL**

**HDL**

**Triglycerides**

**O”bic holic Acid (n = 126)**

**Placebo (n = 131)**

Error bars show 95% CIs; *p<0.05; p-values were derived from linear regression modelling change as a function of treatment group and the baseline value of the outcome; Neuschwander-Tetri BA, et al. Lancet. 2014:S0140-6736(14)61933-4.
OCA Induces Rapid but Reversible LDL-C Increase

No Statin

Baselgline Statin

New Statin

No statin ***p<0.0001, baseline statin †p=0.0597, new statin **p=0.0016; sample only includes patients with both baseline and week 12 LDL-C levels available; ANCOVA model on LDL-C change from baseline at week 72 with baseline LDL-C level as a covariate, statin use, treatment group, and interaction of statin use with treatment group as fixed effects (least squares mean LDL-C change from baseline at week 72 for OCA treatment group); Intercept post hoc analyses.

The REGENERATE Study
RandomizEd Global Phase 3 Study to Evaluate the Impact on NASH with FibRosis of Obeticholic Acid TreatmEnt

2065 patients with biopsy-confirmed NASH; F1–3

1:1:1

Placebo

OCA 10 mg

OCA 25 mg

Study Period (Months)

Screen* 0 18 48 EOS

Interim analysis 1

Interim analysis 2

Accrual of pre-specified number of events†

*NASH confirmed by biopsy ≤6 months before Day 1. †Placebo and OCA 25-mg groups only.

Abbreviations: EOS, end of study; OCA, obeticholic acid.
GFT505, New Dual PPARα/δ–non PPARγ Compound

- Extensive enterohepatic cycling and liver targeted
- No induction of PPAR α or δ genes in muscle
- No PPAR γ activity (no adiponectin induction)

Phase II studies

- Improvement of glucose homeostasis & insulin sensitivity
- Favorable effects on plasma lipids
- Absence of safety concern
- Anti-inflammatory properties
- Improvement of markers of liver dysfunction
- Efficacy on histological NASH parameters in disease models (fibrosis, steatosis, ...)

GFT505-212-7 GOLDEN Study: Phase IIb Trial Design

- **3 parallel groups:** placebo, elafibranor (GFT505) 80mg & GFT505 120mg (secondarily after interim safety analysis of 80 mg) once daily for **52 weeks**
- **274 patients** with histological diagnosis of NASH
- **74-90 clinical centres** distributed in **Europe + US**
- Data Monitoring Committee for safety & efficacy

### Study Design

- **Liver Biopsy**
  - Mth 0
  - Mth 12

- **Screening period & Wash Out**
- **Fenofibrate:** 8wk
  - Vit/UCDA 12wks

- **GFT505**
  - 80 mg
  - 120 mg

- **Placebo**

- **Efficacy & Safety markers**
  - AST, ALT, GGT, Fibrotest, ELF test…
  - CK18, adiponectin…
  - Inflammatory markers, Lipids, Glucose…

- **Follow-up**
  - Mth 4
  - Mth 6
  - Mth 8
  - Mth 10
  - Mth 12

**Ratziu, Gastroenterology 2016**
### Results 1. Resolution of NASH w/o Worsening of Fibrosis, ITT (N=274)

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo (N=92)</th>
<th>Elafibranor 80 mg (N=93)</th>
<th>Elafibranor 120 mg (N=89)</th>
<th>OR* (95% CI)</th>
<th>P (120 mg vs. Plb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY ENDPOINT, UPDATED DEFINITION, (% responders)</td>
<td>12 %</td>
<td>13 %</td>
<td>19 %</td>
<td>2.31 (1.02-5.24)</td>
<td>0.045</td>
</tr>
</tbody>
</table>

### Results 2. Exploratory analyses, bNAS>4, N=234

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo (N=92)</th>
<th>Elafibranor 80 mg (N=93)</th>
<th>Elafibranor 120 mg (N=89)</th>
<th>OR* (95% CI)</th>
<th>P (120 mg vs. Plb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY ENDPOINT, UPDATED DEFINITION, (% responders)</td>
<td>9 %</td>
<td>13 %</td>
<td>19 %</td>
<td>3.52 (1.32-9.40)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

* 120 mg vs. placebo

Ratziu, *Gastroenterology* 2016
Elafibranor—Phase III RESOLVE-IT Trial

2022 patients with F2–3; 202 patients with F1; all with biopsy-confirmed NASH

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Elafibranor 120 mg</th>
</tr>
</thead>
</table>

Screen* 0

Study Period (Months)

18 Interim analysis

48

EOS

Accrual of pre-specified number of events

*NASH confirmed by biopsy ≤6 months before randomization.
Abbreviations: EOS, end of study.
Targets for Drug Development

- 1st generation FXR agonists and PPARs
- Second wave FXR agonists, Pan-PPAR
- Metabolic regulators
  - FGF-19
  - FGF-21
  - SCD-1 inhibitors (Aramchol)
- Anti-inflammatory agents
  - CCR2, CCR5 receptor blockers
  - VAP1 inhibitors
  - Anti-endotoxin compounds
- Anti-fibrotic agents
  - Simtuzumab
  - Galectin 3 inhibitor
EASL–EASD–EASO Clinical Practice Guidelines

of non-alcoholic fatty liver

European Association for the Study of the Liver (EASL)*, 1 of Diabetes (EASD) and European Association for

Introduction

The Clinical Practice Guidelines propose recommendations for the diagnosis, treatment and follow-up of non-alcoholic fatty liver disease (NAFLD) patients, and are the product of a joint effort by the European Association for the Study of the Liver (EASL), European Association for the Study of the Liver and European Association for the Study of Obesity (EASO). They update a position statement based on the 2009 EASL Special Conference [1].

The data have been reviewed by an extensive PubMed search up to April 2015. The final statements are graded according to the level of evidence and strength of recommendation, which are adjustable to local regulations and/or team capacities.

Definition

NAFLD is defined as: (1) steatosis or inflammation + hepatocyte ballooning and/or Mallory-Denk bodies; (2) exclusion of viral hepatitis; (3) exclusion of significant history of ethanol exposure, obesity, type 2 diabetes, and treatment with steroids or thyroxine.

Clinical Practice Guidelines

EASL–EASD–EASO Clinical Practice Guidelines

for the management of non-alcoholic fatty liver disease

European Association for the Study of the Liver (EASL) - European Association for the Study of Diabetes (EASD) - European Association for the Study of Obesity (EASO)

(1) Springer-Verlag Berlin Heidelberg 2016

Abbreviations

ALT alanine transaminase

BMI body mass index

CAP controlled attenuation parameter

CCR C-reactive protein

CK–18 cytokeratin-18 fragments

CVD cardiovascular disease

EASD European Association for the Study of Diabetes

EASL European Association for the Study of Liver

EASO European Association for the Study of Obesity

ELF enhanced liver fibrosis

FIB–4 fibrosis-4 index

HDL high-density lipoprotein

HOMA–RA homeostasis model assessment of insulin resistance

NASH non-alcoholic steatohepatitis

NAFLD non-alcoholic fatty liver disease

NAS non-alcoholic steatohepatitis

PPAR peroxisome proliferator-activated receptor

RFI relative fibrosis index

SADI Sartorius abnormalities

UDCA ursodeoxycholic acid

Introduction

The Clinical Practice Guidelines (CPG) propose recommendations for the diagnosis, treatment and follow-up of non-alcoholic fatty liver disease (NAFLD) patients and are the product of a joint effort by the European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO). They update a position statement based on the 2009 EASL Special Conference [1].

The data have been reviewed by an extensive PubMed search up to April 2015. The final statements are graded according to the level of evidence and strength of recommendation, which are adjustable to local regulations and/or team capacities [table 1] [2]. In particular, screening for NAFLD in the population at risk should be included in the cost of the available resources, considering the burden for the national healthcare systems and the currently limited effective treatments. The document is intended both for practical use and for advancing the research and knowledge of NAFLD in adults, with specific reference to paediatric NAFLD, whenever necessary. The final purpose is to improve patient care and awareness of the importance of NAFLD, and to assist stakeholders in the decision-making process by providing evidence-based data, which also takes into consideration the burden of clinical management for the healthcare systems.


These Guidelines were developed by the EASL, EASD and EASO, and are being published simultaneously in the Journal of Hepatology, Endocrinology and Obesity Facts.

Electronic supplementary material The online version of this article (10.1007/s00455-016-0692-y) contains supplementary material, which is available to authorized users.

European Association for the Study of the Liver (EASL)
auslif@auslif.org

EASL Office, 7 Rue Daunois, CH 1203 Geneva, Switzerland

Published online: 27 April 2016

© 2016 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
Conclusions

• Liver injury needs to be assessed in overweight/obese patients and patients with diabetes:
  – Screening by LFTs and ultrasound
• Steatosis could worsen IR and trigger the metabolic syndrome
• NAFLD is a cause of liver cirrhosis and primary liver cancer
  – Prognosis depends on the presence of steatohepatitis (NASH) and the fibrosis stage
• Develop clinical care and research networks between liver and endocrine specialists
• There is a need beyond diet and lifestyle modifications for pharmacological agents in patients with NASH
CASE #1
Fatty Liver & HCC

Zobair Younossi MD, MPH, FACG, AGAF, FAASLD

Chairman, Department of Medicine, Inova Fairfax Hospital
Vice President for Research, Inova Health System
Professor of Medicine, VCU-Inova Campus
Affiliate Professor of Biomedical Sciences,
George Mason University
Falls Church, Virginia
56 year old overweight and diabetic man with 10 year history of mild and asymptomatic elevation of aminotransferases
He drinks 1 glass of wine 3 times a week
Does not exercise and does not smoke
Has a history of CAD with a stent placed 3 years ago
No surgical history
Family history of “unknown” liver disease in his mother
Takes metformin and MVI
Extensive work up of elevated liver enzymes excluded other causes of chronic liver disease but established fatty liver by ultrasound
Examination is normal except for mild visceral obesity and BMI of 37
Laboratory tests shows AST 72 and ALT 59
Normal albumin, total bilirubin and CBC
A Fibroscan was done over a year ago consistent with 12 kPa
An ultrasound showed an area of “fat sparing” and a subsequent MRI showed 5.2 cm mass in the right lobe of the liver
Doppler US of hepatic vasculature was normal and his AFP was 8
WHAT DO WE DO NEXT?
NAFLD and HCC

- Several case reports and case series of well documented cases of HCC in NAFLD patients
- NAFLD is the third most common cause of HCC
- Cumulative incidence of HCC in NASH cirrhosis is 2.6% as compared to 4% in HCV
  - Absolute Risk for NAFLD-HCC: 3-6% over 8.2-21 years
  - NAFLD-HCC Mortality: 0.25%-2.3% over 8.3-13.7%
- Characteristics:
  - More males (73%), average age 67
  - Single lesion (76%) well to moderately differentiated
  - Larger tumors than viral hepatitis and ALD: 12.8 cm vs. 8.8 cm vs. 7.7 cm (p=0.001)
- SEER 2004–2009 (HCC=4,979 and non-HCC=14,937)
  - Within 1-yr of Diagnosis, fewer HCV/HBV than NAFLD (53% vs. 61%, p<0.05)
  - In addition to age, ESRD, advanced HCC, disease severity, ALD (HR 1.27 (1.06-1.54) and NAFLD 1.21 (1.01-1.45) were independently associated with mortality within 1-yr
- NAFLD-HCC (n=145) and HCV-HCC (n=611)
  - NAFLD-HCC: More metabolic condition, larger tumor & infiltrative pattern
  - HCC found more often outside surveillance in NAFLD than in HCV
  - Cirrhosis present in 50% of NAFLD-HCC patients and nearly all HCV-HCC patients, determined clinically (Path for 35% of cases)

After controlling for confounders, the mean survival was no longer different
NAFLD and Non-cirrhotic HCC

- 1500 VA patients & HCC (2005-2010)
  - Patients without cirrhosis were assigned into 2 categories
    - 43/1500 HCC (2.9%) level 1 evidence no cirrhosis (very high prob)
    - 151/1500 (10.1%) level 2 evidence no cirrhosis (high prob)
  - About 13% of patients with HCC in the VA system do not have cirrhosis.
  - Risk of having HCC in the absence of cirrhosis
    - NAFLD: Unadj OR: 5.4; 95% CI (3.4–8.5)
    - MS: Unadj OR: 5.0; 95% CI (3.1–7.8)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Total</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guzman et al, 2008</td>
<td>Retrospective</td>
<td>HCC patients</td>
<td>50/50</td>
<td>Advanced HCC and MS with bland steatosis</td>
</tr>
<tr>
<td>Paradis et al, 2009</td>
<td>Case series</td>
<td>Surgical HCC w/MS</td>
<td>128/128</td>
<td>MS free of fibrosis (F0/F2: 65% vs. 26%, p &lt; 0.001)</td>
</tr>
<tr>
<td>Hashimoto et al, 2009</td>
<td>Prospective cohort</td>
<td>NASH patients</td>
<td>382/34</td>
<td>Advanced fibrosis RF for HCC (F3/F4 in 88% of HCC vs. 31% in the NASH</td>
</tr>
<tr>
<td>Kawada et al, 2009</td>
<td>Case series</td>
<td>HCC from hepatic resection 1990-2006</td>
<td>1168/1168</td>
<td>6 (75%) of the NASH patients had no cirrhosis with F2 (5) and F3 (1)</td>
</tr>
<tr>
<td>Starley et al, 2010</td>
<td>Summarized case reports</td>
<td>Case reports of HCC in setting of NASH</td>
<td>67/67</td>
<td>15 Patients had no cirrhosis, with 64% having diabetes and 58% obesity.</td>
</tr>
<tr>
<td>Tokushige et al, 2011</td>
<td>Survey</td>
<td>Survey of HCC patients. Among them, 292 had NAFLD-HCC.</td>
<td>14,530/14,530</td>
<td>Among the NAFLD-HCC patients, 38% had no cirrhosis.</td>
</tr>
<tr>
<td>Yasui et al, 2011</td>
<td>Case series</td>
<td>HCC patients with NASH</td>
<td>87/87</td>
<td>Among those 87 patients, 10 were F1, 15 were F2, and 18 were F3</td>
</tr>
<tr>
<td>Duan et al, 2012</td>
<td>Pooled analysis of 25 studies</td>
<td>Patients with NAFLD-associated HCC</td>
<td>169/169</td>
<td>20 patients had F0/F1 and 149 had NASH. 40.2% of the patients developed HCC without cirrhosis</td>
</tr>
<tr>
<td>Mitta et al, 2014</td>
<td>Retrospective cohort</td>
<td>1,500 HCC veteran patients</td>
<td>1500</td>
<td>Patients with NAFLD-related HCC were less cirrhotic (58.3% vs. 72.4% and 85.6%, p &lt; 0.05) of 54 (15%) were not cirrhotic, had larger mean tumor diameter at diagnosis than cirrhotic (p = 0.041)</td>
</tr>
</tbody>
</table>

HCC seems to occur in non-cirrhotics with NAFLD but the incidence must be very low.
## HCC and Diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Total/HCC</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adami et al, 1996</td>
<td>Population-based cohort</td>
<td>Patients with DM between 1965-1983</td>
<td>153,852/533</td>
<td>Overall SIR for primary liver cancer was 4.1</td>
</tr>
<tr>
<td>Wideroff et al, 1997</td>
<td>Population-based</td>
<td>Patients with DM 1977-1989</td>
<td>109,581/258</td>
<td>HCC SIR for DM 4.0 (3.5–4.6)</td>
</tr>
<tr>
<td>Lagiou et al, 2000</td>
<td>Case-control</td>
<td>Patients with HCC 1995-1998</td>
<td>693/333</td>
<td>Patient with history of DM had an OR of 1.86 (95% CI = 0.99–3.51) for HCC</td>
</tr>
<tr>
<td>Bugianesi et al, 2002</td>
<td>Case-control</td>
<td>HCC patients with CC vs. controls</td>
<td>138/138</td>
<td>DM more common in CC (50%) than controls (20%, p = 0.0034)</td>
</tr>
<tr>
<td>El-Serag et al, 2004</td>
<td>Retrospective cohort</td>
<td>Veteran patients with and without DM 1985-1990</td>
<td>824,263/832</td>
<td>Incidence rate for HCC was 2.39 among patients with diabetes vs. 0.87 per 10,000 person-years</td>
</tr>
<tr>
<td>Davila et al, 2005</td>
<td>Case-control</td>
<td>HCC from the SEER-Medicare</td>
<td>8244/2061</td>
<td>DM associated with HCC OR = 3.08 (95% CI =2.74–3.46)</td>
</tr>
<tr>
<td>Chen et al, 2006</td>
<td>Meta-analysis</td>
<td>26 Studies</td>
<td>5138</td>
<td>DM associated with HCC (pooled OR or RR = 2.5)</td>
</tr>
<tr>
<td>Takuma et al, 2010</td>
<td>Case series</td>
<td>11 NASH HCC</td>
<td>11/11</td>
<td>91% had obesity, diabetes, hypertension, or dyslipidemia &amp; 64% had noncirrhotic liver.</td>
</tr>
<tr>
<td>Chen et al, 2010</td>
<td>Population-based cohort</td>
<td>DM compared w matched controls from NHID</td>
<td>1,230,403</td>
<td>DM with cirrhosis had a HR of liver neoplasm of 85.25 (76.84–94.58) compared with controls without risk factors.</td>
</tr>
<tr>
<td>Weizel et al, 2011</td>
<td>Population-based cohort</td>
<td>CC patients from the SEER-Medicare database and controls</td>
<td>199,602/3649</td>
<td>Metabolic syndrome showed an increased risk of HCC (OR = 2.13, 95% CI = 1.96–2.31, p &lt; 0.0001)</td>
</tr>
<tr>
<td>Rosmorduc et al, 2012</td>
<td>Meta-analysis</td>
<td>n/a</td>
<td>n/a</td>
<td>Diabetes remained an independent risk factor</td>
</tr>
<tr>
<td>Turati et al, 2013</td>
<td>Case-control</td>
<td>HCC vs. controls</td>
<td>589/185</td>
<td>Diabetes and obesity were associated to HCC risk with ORs of 4.33 (95% CI 1.89–9.86) and 1.97 (1.03–3.79)</td>
</tr>
</tbody>
</table>

**Diabetes and HCC**

1) DM increases risk 2-3 fold 2) IR….IGF-1

Current Epidemiology and Predictions of NASH and Related HCC

- Patients with NAFLD are at risk for HCC
- Obesity and DM are both associated with increased risk for HCC
- The incidence of HCC in NAFLD, NASH and cirrhosis is not well defined
- Although the rate seem lower than viral hepatitis, given the number of potential patients, NAFLD-HCC will be a major health problem
- HCC can occur in non-cirrhotics with NAFLD
- It is not known if HCC in non-cirrhotic NAFLD is the same entity as NASH cirrhosis-related HCC
- NASH-related HCC may have poorer prognosis
- Screening for HCC in non-cirrhotic NAFLD is not defined
CASE #2

A Patient with Portal Vein Thrombosis and Steatosis

Vlad Ratziu, MD, PhD

Université Pierre et Marie Curie,
Hôpital Pitié Salpêtrière, Paris, France
A 54 Year Old Man with a Diagnosis of Portal Thrombosis

Past history

• 1997: lower left leg thrombosis; no obvious cause
• Consanguinuous parents with history of repeat bouts of thrombosis
• 2 glasses of wine/day; does not smoke
Disease History

• Jan 1998: Mild abdominal pain
  – Upper GI endoscopy: oesophageal varices, medium size, portal hypertensive gastropathy
  – Ultrasound and CT scan of the abdomen: hepatic steatosis (one area); large spleen (16 cm); portal vein cavernoma; signs of portal hypertension
  – CBC: platelet count 74-77 k/mm³

• Specialist referral:
  – The searches for a hypercoagulability state included: (all normal)
    • Protein C, S, antithrombin 3
    • Circulating anticoagulants, anti-phospholipid, anti-cardiolipin, anti-beta 2 glycoprotein antibodies
    • Homocystein, bone marrow aspirate
    • Bone marrow biopsy with culture of erythroblastic progenitors w/wo erythropoietin
  – Secondary causes of steatosis absent: no steatogenic drugs, low cholesterol but no abnormal synthesis of ApoB or ApoB48, ceruleoplasmin normal

• Started on propranolol
Initial Investigations

• Transjugular liver biopsy:
  – Normal hepatic gradient: 4 mm Hg
  – 35 mm long, 5 fragments
  – Macrovacuolar steatosis 80%
  – Mild intralobular and portal lymphocytic infiltrate
  – No portal or perisinusoidal fibrosis
  – NAFL; stage 0
• Second episode of lower limb phlebitis 1999
• D-Dimers 3704 ng/ml (N<500 ng/ml)
• Started on warfarin
Follow-up

- **2005: No further thrombotic events on warfarin**
  - Upper GI endoscopy: small size oesophageal varices
  - 87 kg, 1.79 cm, waist circumference 104 cm
  - AST 32 IU/L, ALT 47 IU/L, GGT 40 IU/L
  - FibroTest 0.54
  - Fibroscan (2007) : 6.1 kPa

- **2010: Asymptomatic**
  - 98 kg; waist circumference 111 cm
  - One glass of wine per day, a few times a week
  - AST 45 IU/L, ALT 57 IU/L, GGT 77 IU/L
  - Serum glucose 5.8 mmol/l; fasting insulin 14.1 µUI/ml, HOMA 3.63
  - FibroTest 0.69; FibroScan 6.9 kPa
Hepatic Reassessment

- **2011**: Increase in Fibrotest 0.70 and Fibroscan 8.1 kPa
- **Liver biopsy, 2011**:
  - Steatosis, macrovacuolar 50%
  - Mild hepatocellular ballooning (no Mallory bodies)
  - Mild lymphocytic infiltrate
  - Mild perisinusoidal fibrosis; no portal fibrosis
  - Steatohepatitis; NAS 4, stage 1A
Liver Disease Progression, 2013

• Biology

• Liver biopsy, 2013:
  – Hepatic gradient 2 mmHg
  – Fragment 20 mm length, 2 fragments, 9 portal spaces
  – Macrovacuolar steatosis 70%
  – Severe hepatocyte ballooning; nascent Mallory bodies
  – Severe lobular inflammation
  – Mild perisinusoidal fibrosis, mild portal fibrosis
  – Steatohepatitis; NAS 7; S3A4F2;
  – Absence of nodular regenerative hyperplasia, oblitative veinopathy, portal veinopathy
Follow-up, 2016

- Upper GI endoscopy: Normal, varices absent
- 72 year old, 90 kg, unhealthy diet, eats between meals
- AST 27 IU/L, ALT 30 IU/L, GGT 42 IU/L
- Glycemia 6.65 mmol/l; insulin 13.4 µUI/L; Cholesterol 1.44 g/l; HDL-C: 0.4 g/l; LDL-C: 0.83 g/l; triglycerides 1.06 g/l
- FibroTest 0.77; Fibroscan 8.1 kPa; XL: 6.3 kPa
In Conclusion: NAFLD a Silent and Overlooked Disease…!

- Repeated thrombotic events including portal thrombosis in a patient with a family history of thrombosis
- No identifiable cause of a hypercoagulable state despite extensive, expensive and lengthy investigations
- Totally overlooked metabolic fatty liver disease…
- Progression from NAFL to highly active steatohepatitis with fibrosis, that paralleled weight gain and unhealthy eating
- No new occurrence of thrombosis and disappearance of endoscopic portal hypertension on life-long anticoagulant therapy
- Take home message: insidious progression of NAFLD while concentrating on unrelated conditions without long-term hepatic consequences!
For the most current information and clinically meaningful education on chronic liver diseases, please visit www.ChronicLiverDisease.org