Best Practices in NASH Management and Current Status of Drug Development

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Disclosures

• Consulting for: Allergan, Astra-Zeneca, Boehringer-Ingelheim, Enanta, Galmed, Genfit, Intercept, Novartis, Pfizer, 89 Bio, Prosciento

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Opinions expressed here are solely based on my own academic views and are intended to stimulate intellectual debate and not in any direct or indirect way drug prescription, clinical trial enrollment for any particular drug or any investment financial or otherwise for drug development programs.
Choice is Yours
Weight Loss Pyramid

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

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%)*

Patients achieving:

*Depending on degree of weight loss.


Slide courtesy of S. Harrison.
Weight Loss and Histological Improvement

- Data are based on a prospective, non-interventional, open-label study into the effects of a low-fat hypocaloric diet, 200 min/week walking and behavioural therapy sessions on liver outcomes in 293 Cuban patients

<table>
<thead>
<tr>
<th></th>
<th>Weight loss &lt; 10% (n = 264)</th>
<th>Weight loss &gt; 10% (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution of NASH</td>
<td>17%</td>
<td>90%</td>
</tr>
<tr>
<td>Fibrosis regression</td>
<td>16%</td>
<td>45%</td>
</tr>
</tbody>
</table>

Resolution of NASH

\[ \text{rho}=0.54, P<0.01 \]

Changes in fibrosis

\[ \text{rho}=0.13, P=0.02 \]
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)

Limitations of a Non-Pharmacological Approach

- Implementation (lack of specialised resources)
- Counter-regulatory mechanisms to increase appetite
- Inter-individual variability in the metabolic response
- Insufficient improvement in patients with advanced liver injury
- Difficulty in maintaining lifestyle changes and associated metabolic effects over time
• A Mediterranean diet is associated with a reduced risk of the metabolic syndrome and each of its components; beneficial effect for central obesity
• Inverse relationship with numerous forms of cancer

IN THE LIVER

Reduces IHTG and IR independent of WL (RCT)
Is associated with reduced risk of being diagnosed with HCC (a 1/3 reduction)

Hepatic Fat Reduction Is Associated with Reduced CV Risk

Independent of VAT changes

278 participants with abdominal obesity/dyslipidemia
18 month RCT: Mediterranean diet vs Low-fat diet

Snacking Significantly Increases Liver Fat Content, Abdominal Fat and Hepatic IR*

6 wk hypercaloric diet.
Independent of caloric content and body weight gain.
**15 Min Exercise Reduces Mortality!**

*Prospective cohort study Taiwan, 416,175 individuals, 8 yr f/u*

**Inactive vs. 15 min:** +17% all-cause mortality; +11% cancer mortality

Addtl 15min exercise:
4% reduction all cause,
1% reduction cancer mortality

Low volume daily exercise post-pones death
1 in 6 all cause
1 in 9 cancer

16 Wk Intensive Lifestyle Intervention and HVPG Reduction

- Compensated cirrhosis of any etiology
- Child A or B8, HVPG > 6 mmHg
- BMI > 26 kg/m²
- Reduction in caloric intake 500-1600 kCal/d
- 1/wk 60 min supervised exercise

42% of Pts had a reduction in HVPG > 10%
Incl. 24% with a decrease > 20%

A > 10% WL for a greater reduction in HVPG

### Available Drugs with Reported NASH Efficacy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rationale</th>
<th>Efficacy (level of evidence)</th>
<th>Side Effects</th>
<th>Definitive Demonstration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pioglitazone</td>
<td>++</td>
<td>adipose IR</td>
<td>High</td>
<td>Weight gain, Fractures, Heart failure</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>+</td>
<td>antiox</td>
<td>Medium</td>
<td>Prostate CV, Stroke</td>
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<tr>
<td>UDCA</td>
<td>+, antiox</td>
<td>Cytoprot</td>
<td>Low</td>
<td>None</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>++</td>
<td>Weight loss</td>
<td>Low</td>
<td>GI</td>
</tr>
<tr>
<td>Pentoxyfillin</td>
<td>+/ -</td>
<td>Very Low</td>
<td>Low</td>
<td>GI</td>
</tr>
<tr>
<td>Orlistat</td>
<td>+</td>
<td>Weight loss</td>
<td>Low</td>
<td>GI</td>
</tr>
</tbody>
</table>
Results of the PIVENS trial in non-diabetic NASH

Liver biopsy

96 weeks

Liver biopsy

PLACEBO
N=83

PIOGLITAZONE (30 mg/d)
N=80

Vitamin E (800 mg/d)
N=84

96 weeks

RESOLUTION OF STEATOHEPATITIS

P = 0.05
P < 0.001

Pioglitazone improved:
- Steatosis
- Inflammation
- Ballooning
- NAS score

Sanyal. NASH CRN, NEJM. 2010.
Short and Long-Term Pioglitazone for NASH

• Histologically confirmed NASH
• OGTT: pre-diabetes or diabetes only
• Pioglitazone (30 mg/d then 45 mg/d) vs. placebo
Histological Improvement at 18 Months

- **NAS > 2**
  - Pioglitazone: 58%
  - Placebo: 17%

- **NASH resol**
  - Pioglitazone: 51%
  - Placebo: 19%

- **Inflammation**
  - Pioglitazone: 49%
  - Placebo: 22%

- **Ballooning**
  - Pioglitazone: 51%
  - Placebo: 24%

- **Fibrosis**
  - Pioglitazone: 39%
  - Placebo: 25%

*P = 0.13*
Vitamin E: Efficacy in Combination with Pioglitazone?

105 Pts with NASH and T2DM; 18 mo therapy

**≥ 2 point NAS reduction w/o fib worsening**
- PIO+Vit E: 54 (P = 0.003*)
- Placebo: 31 (P = 0.26*)

**NASH resolution w/o fib worsening**
- PIO+Vit E: 43 (P = 0.005*)
- Placebo: 33 (P = 0.04*)

**≥ 1stage fibrosis improvement**
- PIO+Vit E: 52 (P = 0.07*)
- Placebo: 50 (P = 0.09*)

* vs. Placebo.

Vitamin E Prevents Hepatic Events in Patients with Advanced NASH

90 patients with NASH F3-F4 on Vit E > 2 years,
90 matched controls
5,6 years follow-up

OLT-free: 78% vs 49%

OLT-free: HR 0.3 (0.12 – 0.74, p < 0.01)

Hepatic decompensation: HR 0.52 (0.28 – 0.96, p < 0.04)

No change in HCC risk

Drugs with Collateral Benefits

- **Metformin**
  - Reduced risk of liver cancer?
  - Increased survival in cirrhotics?

- **Statins**
  - Reduced risk of liver cancer?
  - Reduced risk of death and complications in cirrhotics?
  - Reduced portal hypertension?
  - Reduced fibrogenesis?

- **GLP1R agonists and SGLT2 inhibitors**
  - Reduction of CV mortality and events
Metformin Prevents Hepatic Events in T2DM Pts with Advanced NASH

- **OLT-free**
- **Hepatic decompensation**
- **HCC development**

110 T2DM patients with NASH F3-F4 on metformin > 2 years,
81 matched controls
6 years follow-up

Risk of liver cancer was decreased by 91% when metformin was compared to other drugs.

Comparison of metformin vs. sulphonylureas showed a 44% risk reduction.
Drugs with Collateral Benefits

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Non-biliary FXR–FGF19

FXR – FGF19

ANTI-INFLAMMATORY / ANTIFIBROTICS

FXR

Non-biliary FXRs

Emricasan

Galectin

CVC

JNKi

Antioxidants

Emory

CVC

Metacrine

Novartis

Enanta

Older FXRs

FXR – FGF19

NGM282

OCA

PPARS

mTOT

PPARS

Elafibranor

Seladelpar

Saroglitazar

Lanifibranor

Saroglitazar

PPARS

AMPKag

SGLT2i

Semaglutide

& GLP1Rag

Semaglutide

& GLP1Rag

Dual agonists

Astra-Zeneca

Lilly

Seamglutide

& GLP1Rag

SGLT2i

Semaglutide

& GLP1Rag

Semaglutide

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The Month 18 interim analysis was conducted after 931 randomized patients with fibrosis stage 2 or 3 completed their Month 18 or end-of-study visit (ITT population).

EOS analysis of clinical outcomes to confirm clinical benefit.

Patients were stratified by diabetes status and use of glitazones (TZDs) or vitamin E.

**Study success was defined as achievement of one of the two primary endpoints evaluated in the Month 18 Interim Analysis.**

Presented at EASL, April 10-14, 2019; Vienna, Austria.
Fibrosis Improvement by ≥ 1 Stage with No Worsening of NASH (Primary Endpoint: ITT Population)

Population: ITT* (N = 931)

- Placebo (n = 311): 11.9%
- OCA 10mg (n = 312): 17.6%
- OCA 25mg (n = 308): 23.1%

Population: PP (N = 668)

- Placebo (n = 224): 12.9%
- OCA 10mg (n = 226): 20.8%
- OCA 25mg (n = 218): 27.5%

Primary endpoint definition: improvement in fibrosis by ≥1 stage (NASH CRN) with no worsening of lobular inflammation, hepatocellular ballooning or steatosis.

Study success was defined as achievement of one of the two primary endpoints evaluated in the Month 18 Interim Analysis.

*Statistically significant in accordance with the statistical analysis plan agreed with the FDA. All other p values are nominal.

Presented at EASL, April 10-14, 2019; Vienna, Austria.
Shift in Fibrosis by ≥ 1 Stage (Per Protocol Population)

Percentages for improvement or worsening are calculated based on per protocol population with available biopsy at Month 18 (N=656). Data shown for change in fibrosis stage regardless of NASH status. Presented at EASL, April 10-14, 2019; Vienna, Austria.
NASH Resolution with No Worsening of Fibrosis
(Additional Primary Endpoint: ITT Population)

Primary endpoint definition: (i) pathologist overall histopathologic assessment of “no fatty liver disease” or “fatty liver disease (simple or isolated steatosis) without steatohepatitis”; (ii) NAFLD Activity Score (NAS): hepatocellular ballooning = 0 and lobular inflammation = 0 or 1; and (iii) no increase in fibrosis stage from baseline.

Study success was defined as achievement of one of the two primary endpoints evaluated in the Month 18 Interim Analysis. Presented at EASL, April 10-14, 2019; Vienna, Austria.
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
- Improvement of markers of liver dysfunction
- Favorable effects on plasma lipids
- Absence of safety concern
- Efficacy on histological NASH parameters in disease models (fibrosis, steatosis, ...)
- Anti-inflammatory properties

GOLDEN Trial: Results on the Primary Outcome in the ITT and Subpopulations

(Ratziu. Gastroenterology. 2016.)

<table>
<thead>
<tr>
<th>N</th>
<th>NAS</th>
<th>Placebo</th>
<th>Elafibranor 120mg</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>274</td>
<td>All patients (FAS)</td>
<td>12%</td>
<td>19%</td>
<td>0.045</td>
</tr>
<tr>
<td>234</td>
<td>NAS ≥ 4</td>
<td>9%</td>
<td>19%</td>
<td>0.013</td>
</tr>
<tr>
<td>204</td>
<td>NAS ≥ 4 with fibrosis (any stage)</td>
<td>11%</td>
<td>20%</td>
<td>0.009</td>
</tr>
</tbody>
</table>
Extrahepatic, Metabolic Effects of Elafibranor

Elafibranor 120mg vs Placebo on lipid markers

- **: p < 0.01
- ***: p < 0.001

Elafibranor 120mg vs Placebo on glucose homeostasis and insulin sensitivity in type 2 diabetic patients with NASH

- #: p < 0.05
- ##: p < 0.01

Baisse significative de l’HbA1c vs placebo

-0.46%
Resmetirom Is an Oral, Liver Directed, First in Class THR-β Selective Agonist

- MGL-3196 has pleiotropic effects with potential for addressing the underlying metabolic syndrome and hallmark features of NASH; steatosis/lipotoxicity, inflammation, ballooning, fibrosis (both directly and indirectly)
- THR-β agonists reduce liver fat through breakdown of fatty acids, and stimulate mitochondrial biogenesis in the NASH liver, thereby reducing lipotoxicity and improving liver function
- In human NASH, the liver has relatively low THR-β activity, exacerbating mitochondrial dysfunction and lipotoxicity
- THR-β may have direct hepatic and anti-fibrotic effects in that THR agonism has been shown to dampen inflammation in vivo and to inhibit TGF-β signaling in cell culture and in vivo

Effects of Resmetirom on Liver Fat and Lipids

Placebo N=41 or Resmetirom N=84.
12 W (PDFF); 36 w (histology) duration.
Harrison. AASLD. 2018.
SCD1, a Major Target for Metabolic Protection in NAFLD Dietary Models

- Steroyl-CoA desaturase-1 (SCD1) is a key enzyme in hepatic lipogenesis that converts saturated fatty acids into monounsaturated fatty acids
- In high fat or high carb dietary models, down regulation of SCD 1 results in 
  - Resistance to obesity, decreased adiposity
  - Reduced hepatic lipogenesis
  - Enhanced insulin sensitivity
  - Protection from steatosis, hypertriglyceridemia
- Enhanced lipid oxidation

Aramchol for NASH

Multifactorial Effects of GLP1RA

- Increases satiety
- Delays gastric emptying
- Improves lipid profile
- Reduces systemic inflammation
- Reduces Blood pressure

WEIGHT LOSS

GLYCEMIC CONTROL

CV BENEFITS

LIPOGENESIS

IMPROVEMENT IN NASH?

- Insulin secretion
- Glucagon secretion
Conclusions

• The first phase 3 trial results (OCA) are positive for histological (fibrosis) improvement; other phase 3 trials will read out soon or are ongoing

• The interactions between steatohepatitis and fibrosis improvement and their longer term prediction of clinical outcomes need to be understood

• No solid recommendation can be made for currently available drugs

• Statins and metformin should be given in (diabetic) patients with NASH even with advanced fibrotic disease

• Dietary and lifestyle changes are paramount particularly prophylactically

• Many promising drugs in development: distinctions based on fibrotic activity, metabolic effects, route of administration, tolerability