The Expanding World of Fatty Liver Disease

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The Global Epidemic of Obesity is the Main Driver of Global NASH

- Since 1975, worldwide obesity has tripled
  
  WHO 2018

2016 Global Data

- Adults: >1.9 billion (39%) overweight & >650 million (13%) obese
- Children & adolescents (5-19 yrs): 340 million overweight or obese
- Most of the world's population live in countries where overweight and obesity kills more people than underweight.
What Drives the Global Epidemic of Obesity?

**Obesity Is A Complex Disease Related To Genetic And Environmental Factors**

**ENDOCRINE DISEASES**
- Endocrine diseases
  - Hypothyroidism
  - Cushing’s syndrome
  - Growth hormone deficiency
  - PCOS

**MENTAL & PHYSICAL DISABILITY**
- **Mental:** Schizophrenia, downs syndrome, mental illness, learning disabilities, and eating disorders
- **Physical Disability:**
  - Greatly reduced activity levels eg (wheelchair bound) from physical impairments or age
  - Combination of difficulties in regulating food intake & energy output

**GENETIC FACTORS**
- Prader-willi syndrome
- Other syndromes
- Leptin deficiency
- Other defects and deficiencies

**PHYSIOLOGICAL FACTOR**
- Energy intake (more than is needed)
- Energy expenditure
- Thrifty Gene

**ENVIRONMENTAL FACTORS**
- Advertising and marketing of high density foods and soft drinks
- Social deprivation
- Lifestyle changes, more cars etc
- Ethnic tendencies especially if adopting Western lifestyle
- Steatogenic drugs
- Antibiotics in food chain

**SOCIAL FACTORS**
- Reduction in exercise
- Sedentary lifestyle
- TV
- Computer games
- Sedentary jobs
- Fat children become fat adults
- Pregnancy—may eat more or erratically

**BEHAVIORAL FACTORS**
- Consumption of fast food
- Consumption of health unprocessed food
- High sugar and fat diets
- Snacking
- Alcohol consumption
- Weight gain associated with cessation of smoking
- Disorganized eating patterns and eating disorders
NASH in the Context of the Spectrum of NAFLD

Spectrum of NAFLD

NASH

Normal
Steatosis
NASH
NASH with advanced fibrosis
HCC

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis
What are Different Types of Burden in NASH?

**Burden**

- CLINICAL
  - Prevalence and incidence
  - Liver outcomes or surrogates of mortality
  - CVD and other EHM
  - Crude death rates
  - Life-expectancy, expected years of life lost,

- PRO
  - Symptoms
  - HRQOL (Physical, Mental and Social health)

- FUNCTIONAL
  - Functional status (disability)
  - Absenteeism (WP)
  - Presenteeism (WP)
  - Days of work missed
  - Ability to manage ADL

- ECONOMIC
  - Cost of illness
  - Budgetary costs
  - Indirect and intangible costs
  - Resource utilization
  - Cost-effectiveness

**Surrogate Endpoints**

- Survival
- Patient experience
- Feel
- Function and WP
- Resource utilization
- Value

The Global Epidemic of NAFLD and NASH in Adults

- Global prevalence of NAFLD is 25.2%
- Prevalence of NASH in general population is estimated between 1.5% and 6.5%

![Map showing prevalence of NAFLD in different regions]

**Prevalence of NAFLD is Higher in Males and Increases with Age**

The Global Epidemic of NAFLD and NASH in Children
The Most serious Threat!

- Prevalence of NAFLD in US children is 2.6-17.3%
- Autopsy study from UCSD (N=742)
  - Prevalence: 9.6%, rates increasing with age

NAFLD Prevalence in Children
Age 2 to 19 Years per Race/Ethnicity

- More common in Hispanic boys
- Pathology is different: Zone 1 or 3, Mainly portal, Portal-periportal fibrosis, Rare ballooning
- Risks: family history, gestational diabetes, T2D

NAFLD in People with Diabetes

- Systematic review of 49,419 with diabetes in 22 countries
- Overall global NAFLD prevalence among diabetics is 55.5%
- Overall prevalence of NASH in biopsied diabetics is 67.3%
- Overall prevalence of advanced fibrosis (fibrosis ≥ F3) 17.2%

Younossi ZM. J of Hepatology. 2019

NAFLD in Lean Individuals
What Are The Potential Outcomes of NAFLD?

- Normal to Non-NASH
- Non-NASH to NASH
- NASH to NASH with Fibrosis
- NASH with Fibrosis to F1, F2, F3, F4
- F1, F2, F3, F4 to NASH with Fibrosis
- NASH with Advanced Fibrosis
- NASH Patients are at Risk for Cirrhosis, Liver Transplant and liver mortality

- NASH 1.5% and 6.5%
- NAFLD 25%
- The Most Common Cause of Death

- GENOTYPE
  - DNA Sequence

- ENVIRONMENT
  - Diet
  - Microbiome
  - Xenobiotics

- 2.3% per yr
- 0.529% per yr

What are Some Predictors of Adverse Outcomes in NAFLD?

**Presence of NASH Denotes Progressive Disease**
- Biopsy-proven NAFLD (N=289) with 59.2% biopsy-proven NASH
  - After FU 150 months, NASH has higher risk of liver-related mortality than non-NASH ($P=0.003$)

**Increasing Components of Metabolic Syndrome Predicts Mortality**
- NHANES III NAFLD cohort (3,613)
  - Follow-up: December 31st, 2011
  - NAFLD with all MS components associated with overall, CV and liver mortality
  - Lower survival with increasing components of MS ($p<0.001$)

**Stage of Fibrosis Predicts Mortality**
- Systematic review to include 1495 NAFLD patients providing 17,452 patient-years of FU

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The Global Burden of NASH

Worrisome Pattern and Future Predictions
The Epidemic of NAFLD is Growing
The Changing Face of Chronic Liver Diseases in the United States in the Past Three Decades

- 58,731 adult subjects with CLD
- Yearly trend analyses showed that the only liver disease with consistently increasing prevalence was NAFLD (Kendall tau=0.64, P=0.0123)
- In contrast, a decreasing trend was noted for CHC (tau=-0.42, p=0.07).
- **Drivers of NAFLD:** MVA showed that after adjustment for age, gender, and ethnicity, obesity – 10.4 (9.5 - 11.3), T2DM – 3.7 (3.2 - 4.2), hypertension – 2.3 (2.1 - 2.5), hyperlipidemia - 1.8 (1.6 - 2.1)) are major independent predictors of NAFLD.

NAFLD Related Death is on the Rise

- US National Center for Health Statistics multiple-cause mortality data
- Between 2007 and 2017 in the U.S, there were 28,132,187 reported deaths with 700,402 LD-related deaths
  - **Liver Causes of Death (ICD-9 codes)**
  - **Complication of Liver Disease:** 373,345 Cirrhosis; 101,132 HCC; 225,925 no cirrhosis or HCC
  - **Etiology of LD:** 240,961 NAFLD; 197,815 ALD; 73,892 CH-C; 6,375 CH-B; 19,110 other LDs, and 162,249 Unknown.

### 2007 to 2017 (APC)

<table>
<thead>
<tr>
<th>LD severity</th>
<th>Age-standardized-death-rate-per-100,00</th>
<th>Age-standardized-years-of-potential-life-lost-per-1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>16.71 to 18.48 (1.13)</td>
<td>3.68 to 3.84 (0.63)</td>
</tr>
<tr>
<td>HCC</td>
<td>8.79 to 10.51 (1.99)</td>
<td>1.87 to 2.23 (1.99)</td>
</tr>
<tr>
<td>NAFLD</td>
<td>2.18 to 2.78 (1.93)</td>
<td>0.40 to 0.46 (1.08)</td>
</tr>
<tr>
<td>ALD</td>
<td>5.61 to 6.42 (1.48)</td>
<td>1.11 to 1.18 (0.63)</td>
</tr>
<tr>
<td>CH-C</td>
<td>4.50 to 5.96 (3.24)</td>
<td>1.16 to 1.54 (3.24)</td>
</tr>
<tr>
<td>CH-B</td>
<td>2.01 to 1.19 (-5.04)</td>
<td>0.48 to 0.25 (-6.30)</td>
</tr>
<tr>
<td>CH-B</td>
<td>0.23 to 0.13 (-5.35)</td>
<td>0.06 to 0.03 (-6.33)</td>
</tr>
</tbody>
</table>

1. Significantly increasing from 2007 to 2017 (P<.05)
2. Significantly decreasing from 2007 to 2017 (P<.05)
3. Significantly decreasing from 2007 to 2014 (P<.05) and faster decreasing from 2014 to 2017 (P<.05)

Data markers denote observed rates; lines are fitted rates based on joinpoint analysis.


Paik J, Younossi ZM DDW 2019
Future Burden of NASH and Adverse Outcomes in the USA

- **Markov model**
  - Incidence of NAFLD based on historical and projected changes in prevalence of obesity and T2D

≈25-30% of US Adult Population Have NAFLD

- **NAFLD**: 83.1 Million
- **NASH**: 16.5 Million
- **NASH with F3/F4**: 3.3 Million

Unmet Need


By 2030, there are projected to be nearly 800,000 excess liver deaths
Future Burden of NAFLD NASH in Europe and Asia: Prevalence

Estimated number with NAFLD in the USA and EU: 155.4 million

Estimated number with NASH in the USA and EU: 28.9 million

Estimated number of F3/F4 fibrosis due to NASH in the USA and EU: 5.8 million

Future Burden of NASH in Europe and Asia: Adverse Outcomes

Estes et al. J Hepatol 2018;69:896
Non-Hepatic Diseases Associated with NAFLD

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>FU (yr)</th>
<th>CVD Death</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angulo, 2015</td>
<td>619</td>
<td>12.6</td>
<td>38.3%</td>
<td>CVD most common COD Fibrosis predicts death</td>
</tr>
<tr>
<td>Söderberg, 2010</td>
<td>118</td>
<td>24</td>
<td>30%</td>
<td>Death in NASH, CVD most common COD</td>
</tr>
<tr>
<td>Ekstedt, 2006</td>
<td>129</td>
<td>13.7</td>
<td>16%</td>
<td>CVD death NASH CVD most common COD in NASH but no SS</td>
</tr>
<tr>
<td>Dam-Larsen, 2009</td>
<td>170</td>
<td>20.4</td>
<td>38%</td>
<td>No difference between SS and control</td>
</tr>
<tr>
<td>Rafiq, 2009</td>
<td>173</td>
<td>18.5</td>
<td>12.7%</td>
<td>CVD most common COD</td>
</tr>
</tbody>
</table>

Patient Characteristic | NAFLD (n=3869) | Control (n=15,209) | Fold Increase |
-----------------------|---------------|-------------------|--------------|
Median age, yrs        | 53            | NR                |              |
Women, %               | 52            | NR                |              |
Diagnosed with malignancy, n (%) | 580 (15)       | 1521 (10)        |              |
Site of malignancy, incidence/100,000 PY |                  |                  |              |
- Liver                | 26.8          | 6.6              | 4            |
- Stomach              | 9.8           | 2.8              | 3.5          |
- Pancreas             | 19.6          | 7.2              | 2.7          |
- Lung                 | 34.1          | 16.9             | 2            |

COD, cause of death; CVD, cardiovascular disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; SS, simple steatosis
NASH with Advanced Fibrosis Have Impaired Patient Reported Outcomes

- Biopsy proven NASH (N=1667 from STELLAR with PROs

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<tr>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Mean PRO score, 0-100 scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Bridging fibrosis</td>
<td>population norm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| p<0.05 b/w cirrhosis and bridging fibrosis

- NASH with Stage 2–3 fibrosis (N=72):

Mean PRO score, 0-100 scale

Economic models to assess burden of NAFLD using interlinked Markov chains

- Over 64 million people with NAFLD, with annual direct medical costs of about $103 billion

Economic burden of NASH

- Markov models (prevalence and incidence)
- In the U.S., there are 688 thousand cases of advanced NASH
- Lifetime direct costs of all NASH will be $222.6 billion
- Lifetime direct costs of the advanced NASH population will be $95.4 billion.

Markov Model Structure

NASH Patients with Advanced Fibrosis have the Profound Economic Impact

To address increased CV mortality risk all NAFLD subjects are candidates for life style modification and treatment of metabolic risk factors.

To address the increased risk of liver-related mortality, NASH subjects should be considered treatment candidates.

NASH patients with advanced fibrosis are at most urgent need for treatment.

How to identify and stage NASH?

What is the current evidence for treatment of NASH?
# Diagnostic Tests for NAFLD

<table>
<thead>
<tr>
<th>NAFLD</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liver Enzymes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ALT</td>
<td>45%</td>
<td>85%</td>
</tr>
<tr>
<td>• GGT&lt;sup&gt;1&lt;/sup&gt;</td>
<td>63%</td>
<td>65%</td>
</tr>
<tr>
<td><strong>Ultrasound&lt;sup&gt;2&lt;/sup&gt;</strong></td>
<td>85%</td>
<td>94%</td>
</tr>
<tr>
<td>• Any degree&lt;sup&gt;3&lt;/sup&gt;</td>
<td>61%</td>
<td>100%</td>
</tr>
<tr>
<td>• Cutoff ≥ 20%&lt;sup&gt;3&lt;/sup&gt; CT without contrast&lt;sup&gt;4&lt;/sup&gt;</td>
<td>100%</td>
<td>90%</td>
</tr>
<tr>
<td>• <strong>Cutoff &gt; 30%</strong></td>
<td>79%</td>
<td>97%</td>
</tr>
<tr>
<td><strong>MRI&lt;sup&gt;5&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cutoff PDFF 6.4%, grade ≥1</td>
<td>86%</td>
<td>83%</td>
</tr>
<tr>
<td>• Cutoff PDFF 17.4%, grade ≥2</td>
<td>64%</td>
<td>96%</td>
</tr>
<tr>
<td><strong>Spectroscopy</strong></td>
<td>~100%</td>
<td>~100%</td>
</tr>
<tr>
<td><strong>Liver Biopsy</strong></td>
<td>98% to 100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

---

**Diagnostic Tests for NASH**

<table>
<thead>
<tr>
<th>NASH</th>
<th>Study</th>
<th>AUROC</th>
<th>AUROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASH</td>
<td>Feldstein, et al. CK-18</td>
<td>0.83</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>Feldstein, et al. CK-18, sFasL</td>
<td>0.93</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td>Feldstein, et al. oxNASH (13-HODE/LA, age, BMI, AST)</td>
<td>0.83</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Younossi, et al. NASH diagnostics</td>
<td>0.98</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>Poynard, et al. NASH test</td>
<td>0.79</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>Palekar, et al. HA + clinical</td>
<td>0.76</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Loomba, et al. Lipidomic</td>
<td>1.00</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Noninvasive Diagnosis of Liver Fibrosis
Commonly Used Fibrosis Scores

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FIB-4 Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td></td>
</tr>
<tr>
<td>Platelet count, cells x 10⁹</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td></td>
</tr>
<tr>
<td>Impaired fasting glucose/DM?</td>
<td></td>
</tr>
</tbody>
</table>

**NAFLD Fibrosis Score**

<table>
<thead>
<tr>
<th>NFS Cutoff Value¹</th>
<th>Stage</th>
<th>FIB-4 Cutoff Value²</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;-1.455</td>
<td>F0–F2</td>
<td>1.45</td>
<td>F0–F2</td>
</tr>
<tr>
<td>-1.455 to 0.676</td>
<td>Indeterminate</td>
<td>1.45 to 3.25</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>&gt;0.676</td>
<td>F3–F4</td>
<td>&gt;3.25</td>
<td>F3–F4</td>
</tr>
</tbody>
</table>

**FIB-4 Formula**

\[
\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count (10⁹/L) \times \sqrt{\text{ALT (U/L)}}}}
\]

**APRI Formula**

\[
\text{APRI} = \frac{(\text{AST Level (U/L)})}{(\text{Platelet Count (10⁹/L) \times \text{ALT (U/L)}}} \times 100
\]

**APRI**:
The lower the APRI score (<0.5), the greater the NPV (and ability to rule out cirrhosis) and the higher the value (>1.5) the greater the PPV (and ability to rule in cirrhosis).

Noninvasive Diagnosis of Liver Fibrosis
Radiologic Tests To Measure Liver Stiffness or Elasticity

<table>
<thead>
<tr>
<th>Technique</th>
<th>Visualize liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient elastography (TE)</td>
<td><strong>Liver stiffness</strong> expressed in kPa; correlates with liver fibrosis stage</td>
</tr>
<tr>
<td></td>
<td>• Controlled Attenuation Parameter (CAP™) expressed in dB/meter</td>
</tr>
<tr>
<td></td>
<td>• Accurate in detecting advanced fibrosis</td>
</tr>
<tr>
<td></td>
<td>• Predicts risk of decompensation</td>
</tr>
<tr>
<td></td>
<td>• Correlates well with portal pressure</td>
</tr>
<tr>
<td></td>
<td>• Most widely used</td>
</tr>
<tr>
<td>Acoustic radiation force impulse (ARFI)</td>
<td><strong>Employs high intensity acoustic beam to mechanically excite tissue and monitor tissue displacement response</strong></td>
</tr>
<tr>
<td></td>
<td>• No need for an external compression</td>
</tr>
<tr>
<td></td>
<td>• Degree of displacement is interpreted into degree of lightness and darkness</td>
</tr>
<tr>
<td>Shear wave elastography (SWE)</td>
<td><strong>Shear waves are generated from acoustic pulses forced at five different tissue depth levels and SW velocity estimated by ultrafast Doppler-like acquisition of 5,000 frames/sec.</strong></td>
</tr>
<tr>
<td></td>
<td>• SW is converted to tissue stiffness as kilopascals</td>
</tr>
<tr>
<td>Magnetic resonance elastography (MRE)</td>
<td><strong>Most accurate of the imaging modalities</strong></td>
</tr>
<tr>
<td></td>
<td>• Costly, no point-of-care access</td>
</tr>
<tr>
<td></td>
<td>• MRI Methods to Estimate Proton Density Fat Fraction</td>
</tr>
<tr>
<td></td>
<td>• MRI-PDFF shown to have high correlation to morphometric fat³</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fibrosis Severity</th>
<th>Median LSM (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without F3-F4 fibrosis</td>
<td>6.6 kPa (5.3-8.9)</td>
</tr>
<tr>
<td>With F3-F4 fibrosis</td>
<td>14.4 kPa (12.1-24.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median Values</th>
<th>Stiffness cutoff: 3.63 kPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0</td>
<td>6.93 kPa</td>
</tr>
<tr>
<td>F1</td>
<td>7.7 kPa</td>
</tr>
<tr>
<td>F2</td>
<td>9.6 kPa</td>
</tr>
<tr>
<td>F3</td>
<td>13.95 kPa</td>
</tr>
<tr>
<td>F4</td>
<td>23.73 kPa</td>
</tr>
</tbody>
</table>
MRI More Accurate Than Transient Elastography in Steatosis and Liver Fibrosis

- 142 patients with NAFLD (biopsy-proven; BMI 28.1 kg/m²)
- FIB-4 had the highest diagnostic performance to assess liver fibrosis

In Japanese patients with NAFLD, MRE had higher diagnostic accuracy for fibrosis relative to scoring systems and TE.

MRE-PDFF was superior to CAP for steatosis grade.


- MRE
- SWE
- VCTE/fibroscan
Suspected NAFLD
Hepatic steatosis on imaging with elevated serum ALT

Evaluate alcohol consumption

Confirmation of NAFLD

Exclude alternative causes of ↑ ALT

Noninvasive risk stratification

Low-risk profile
- BMI <29.9
- Age <40 years
- Absent T2DM or metabolic syndrome
- Low FIB4, APRI, and NFS
- Normal or elevated ALT
- Fibroscan® <6 kPa
- Most likely steatosis only

Intermediate-risk profile
- BMI >29.9
- Some metabolic syndrome features
- FIB4 <3, APRI <1.5, NFS =1.454-0.676
- Elevated ALT
- Fibroscan® 7-10 kPa
- Possibly NASH with <F3

High-risk profile
- Age >50 years
- T2DM
- FIB4 >3, APRI >1.5, NFS >0.676
- Elevated ALT
- Fibroscan® >10 kPa
- Most likely F3-F4
- Consider biopsy if clinical trials

If noninvasive profile indeterminate, obtain liver biopsy and combine results with noninvasive tests
Integrated Treatment Strategies for NAFLD and NASH

Public Health Interventions

Multi-prong Approach to Manage Obesity

Therapeutic Targets:
- Improving Hepatic Metabolism
- Improving insulin sensitivity
- Improving inflammation
- Improving fibrosis

Patient Target:
- NASH
- NASH with Advanced Fibrosis
Integrated Treatment Strategies for NAFLD and NASH

Public Health Interventions

Multi-prong Approach to Manage Obesity

Current Therapeutic Options:
- Weight loss with diet
- Exercise
- Weight loss procedures
- Currently available medications

Patient Target:
- NASH
- NASH with Advanced Fibrosis
**Current Management of NAFLD and NASH**  
*Weight Loss: Success and Impact on Fibrosis*

### Probability of improving NASH components according to weight loss

- **52 weeks of lifestyle intervention**

<table>
<thead>
<tr>
<th>% Weight Loss (WL)</th>
<th>5%</th>
<th>7%</th>
<th>10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASH Resolution</td>
<td>10%</td>
<td>26%</td>
<td>64%</td>
</tr>
</tbody>
</table>

### AASLD Guidance 2018  
*Weight Loss and Exercise*

- **Weight loss**
  - 3%-5% to improve steatosis, but 7%-10% to improve the majority of the histologic features of NASH, including fibrosis

- **Sustainability of weight loss:**
  - Seven trials, total of 373 patients

---

**Weight loss can be effective but hard to achieve and sustain**

**Exercise alone may prevent or reduce steatosis, but its ability to improve other aspects of liver histology remains unknown**

Current Management of NASH

Bariatric Procedures

- NASH (N=21) treated endoscopically with Orbera™ Intragastric Balloon (Apollo Endosurgery, Austin, TX)
- EUS-liver biopsy and MRE at the time of placement and removal
- Total body weight loss 12.8% (0–32.5)
- NAS ≥2 improvement 73%
- Fibrosis improved in 20%
- MRE and PDFF improved

MRE-PDFF Pre- and Post-IGB Placement

Biopsies courtesy of Dr. Prithi Bhathal 2011; EUS, endoscopic ultrasound; IGB, intragastric balloon; MRE, magnetic resonance elastography; NAFLD, non-alcoholic fatty liver disease; NAS, NAFLD Activity Score; NASH, non-alcoholic steatohepatitis; PDFF, proton density fat fraction

Pharmacologic Treatment for NAFLD and NASH
Currently, No Approved Drug!

Not FDA Approved but AASLD Guidance Supports Use

- Pioglitazone
- Vitamin E

Products of Significant Interest but Evidence is not Available

- GLP-1 Agonist
- SGL2 Inhibitors

Current Evidence Does not Support Efficacy for Treating NASH

- Caspase inhibitors
- Ursodeoxycholic acid
- Anti-obesity medications
- Betaine
- N-Acetyl-cysteine
- Lecithin
- Silymarin
- Beta-carotene
- Omega 3 Fatty Acid (Pufa, ‘Fish Oil’)
- Anti-TNF agents (Pentoxifylline)
- ACE inhibitors/ARBs
- Metformin
- Probiotics (VSL#3)
- Lipid Lowering agents (statins)
## Current Management of NASH

**Vitamin E**

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Dose</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arendt</td>
<td>80</td>
<td>1000 IU/d</td>
<td>Placebo</td>
<td>Improved steatosis (assessed by CT scan) vs placebo</td>
</tr>
<tr>
<td>Sanyal</td>
<td>247</td>
<td>800 IU/d</td>
<td>Pioglitazone, placebo</td>
<td>Improved steatosis, inflammation, and ballooning vs placebo</td>
</tr>
<tr>
<td>Lavine</td>
<td>173</td>
<td>800 IU/d</td>
<td>Metformin, placebo</td>
<td>Improved steatohepatitis and ballooning vs placebo</td>
</tr>
<tr>
<td>Harrison</td>
<td>45</td>
<td>1000 IU/d</td>
<td>Placebo</td>
<td>Improved fibrosis vs baseline</td>
</tr>
</tbody>
</table>

- **AASLD Guidance document:**
  - Vitamin E: At 800 IU/day improves histology in nondiabetic with NASH
  - Risks and benefits should be discussed
  - Not recommended for NASH in diabetic patients, NAFLD without a liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis
Current Management of NASH

**PPAR-γ Agonist**

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Drug</th>
<th>Time</th>
<th>DM</th>
<th>Cirrhosis</th>
<th>ALT</th>
<th>Fat</th>
<th>BaI</th>
<th>Infl</th>
<th>Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caldwell</td>
<td>10</td>
<td>Troglit 400 mg</td>
<td>3-6 months</td>
<td>1/10</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>No</td>
<td>?Yes</td>
<td>No</td>
</tr>
<tr>
<td>Promrat</td>
<td>18</td>
<td>Pio 30 mg</td>
<td>12</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Aithal</td>
<td>7</td>
<td>Pio 30 mg</td>
<td>12 mo</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Belfort</td>
<td>5</td>
<td>Pio 45 mg</td>
<td>6 mo</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Ratziu</td>
<td>6</td>
<td>Rosi 8 mg</td>
<td>12 mo</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Sanyal</td>
<td>2</td>
<td>Pio 30 mg</td>
<td>96 wk</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>---</td>
<td>Yes</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Mahady</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

Current Management of NASH

Pioglitazone in NASH

- Potential AEs: bone loss, diastolic dysfunction, weight gain?
- Pioglitazone-AASLD 2018
  - Pioglitazone improves liver histology in patients with and without T2DM with biopsy-proven NASH
  - Risks and benefits should be discussed with each patient
  - Should not be used for NAFLD without biopsy-proven NASH
Current Management of NASH
Lipid Lowering Agents

- Patients with NAFLD or NASH are not at higher risk for serious liver injury from statins
- Statins can be used to treat dyslipidemia in patients with NAFLD and NASH
- While statins may be used in patients with NASH cirrhosis, they should be avoided in patients with decompensated cirrhosis
- No indication for treatment of NASH

AASLD Guidance 2018

<table>
<thead>
<tr>
<th>Study</th>
<th>Design (mts)</th>
<th>Meds</th>
<th>N</th>
<th>ALT</th>
<th>Hist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laurin</td>
<td>Open label (12)</td>
<td>Clofibrate</td>
<td>16</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Fernández- Miranda C</td>
<td>Open label (12)</td>
<td>Fenofibrate</td>
<td>16</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Basaranoglu</td>
<td>RCT (1)</td>
<td>Gemfibrozil</td>
<td>46</td>
<td>+</td>
<td>NA</td>
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<tr>
<td>Horlander</td>
<td>Open label (12)</td>
<td>Atrovastatin</td>
<td>7</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Kiyici</td>
<td>Open label (6)</td>
<td>Atrovastatin</td>
<td>27</td>
<td>+</td>
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<tr>
<td>Hatzitolios</td>
<td>Open label (6)</td>
<td>Atrovastatin</td>
<td>35</td>
<td>+</td>
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<tr>
<td>Gomez- Dominguez</td>
<td>Open label (12)</td>
<td>Atrovastatin</td>
<td>25</td>
<td>+</td>
<td>NA</td>
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<tr>
<td>Rallidis</td>
<td>Open label (7)</td>
<td>Pravastatin</td>
<td>5</td>
<td>+</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Integrated Treatment Strategies for NAFLD and NASH

Multi-prong Approach to Manage Obesity

Public Health Interventions

Therapeutic Targets:
- Improving Hepatic Metabolism
- Improving insulin sensitivity
- Improving inflammation
- Improving fibrosis

Patient Target:
- NASH
- NASH with Advanced Fibrosis
DAMP, danger-associated molecular patterns; ECM, extracellular matrix; IL-1β, interleukin-1beta; PAMP, pathogen-associated molecular patterns; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor beta; TNF, tumor necrosis factor; TNF-β, tumor necrosis factor-beta.

Some of New Targets for Treatment of NASH

**TARGETS RELATED TO INSULIN RESISTANCE AND/OR LIPID METABOLISM**
- **PPARγ**: Pioglitazone
- **GLP-1**: Liraglutide
- **MPCi**: PXL065
- **SGLT1/2**: LIK066
- **ACCi**: GS-0976, PF-05221304
- **DGAT2i**: PF-06865571
- **SCD1**: Aramchol
- **FGF21**: BMS-986036

**TARGETS RELATED TO LIPOTOXICITY & OXIDATIVE STRESS**
- **PPARα/δ**: Elafibranor
- **PPARα/δ/γ**: IVA337
- **PPARα/γ**: Saroglitazar
- **THRβ**: MGL-3196
- **mTOT**: MSDC-0602K
- **FXR**: OCA, GS-9674,
- **TGR5**: INT-767, INT-777
- **DGAT2i**: PF-06865571
- **SCD1**: Aramchol
- **FGF21**: BMS-986036

**TARGETS RELATED TO INFLAMMATION AND IMMUNE ACTIVATION**
- **CCR2/5**: Cenicriviroc
- **AOC3**: BI 1467335
- **TLR4**: JKB-121
- **Anti-LPS**: IMM-124E

**TARGETS RELATED TO CELL DEATH (APOPTOSIS AND NECROSIS)**
- **ASK1**: Selonsertib
- **Caspases**: Emricasan

**TARGETS RELATED TO FIBROGENESIS & COLLAGEN TURNOVER**
- **LOXL2**: Simtuzumab
- **Galectin**: GR-MD-02

**Normal Liver**

**Steatosis without NASH**

**NASH**

**Cirrhosis**
Regimens in Development for Treatment of NASH

- Many drugs under evaluation for treatment of NASH
  - >85 clinical trials (active or planned)
  - 4 Phase 3 Clinical Trials

**GOLDEN 505-Peroxisome Proliferator-Activated Receptors (PPAR α/δ Pathways) Elafibranor**

### Protocol-defined primary end point

- Placebo (n=92)
- Elafibranor 80 mg (n=93)
- Elafibranor 120 mg (n=89)

### Updated definition

- OR (95% CI) 1.53 (0.70–3.34), \( P=0.28 \)
- OR (95% CI) 2.31 (1.02–5.24), \( P=0.045 \)

### Patients, %

- Placebo (n=92): 17
- Elafibranor 80 mg (n=93): 23
- Elafibranor 120 mg (n=89): 21

### RESOLVE-IT: Long-Term Evaluation of Elafibranor for NASH

- Placebo
- Elafibranor 120 mg

### Study Period (Months)

- Week 18
- Week 48
- End of Study (EOS)

### Screen

- 2022 patients with F2-3
- 202 patients with F1
- All with biopsy-confirmed NASH

### Notes

- \( a < 0.05 \) vs placebo
- \( b < 0.01 \) vs placebo
- Resolution of NASH without worsening of fibrosis at EOS
- More stringent definition of resolution of NASH recommended by regulatory agencies
- NASH confirmed by biopsy ≤ 6 months before randomization

---

N=242 patients with NASH continued to year 2. Patients underwent biopsies at baseline, year 1, and year 2 to assess fibrosis, NASH, and NAS.

NASH-AURORA Study

Primary Endpoint at Year 1: improvement in fibrosis AND no worsening of NASH (N ≥ 1000)

N=144

Year 1 Results

- Placebo: 19
- CVC: 16

P=0.519

≥2-Point Improvement in NAS AND No Worsening of Fibrosis

Placebo QD

CVC 150 mg QD

Screening Biopsy

Biopsy at Month 12

CVC 150 mg QD

Placebo QD

Biopsy at Month 60

Year 2 Results

- Placebo: 30
- CVC: 60

P=0.023

≥2 stage fibrosis improvement AND No Worsening of Fibrosis

Obeticholic Acid: FLINT and REGENERATE Studies

**Improvements in Histology over 72 Weeks**

- Obeticholic acid
- Placebo

<table>
<thead>
<tr>
<th>Condition</th>
<th>Obeticholic acid</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histological improvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resolution of NASH</td>
<td>a</td>
<td></td>
</tr>
<tr>
<td>Improvement in fibrosis</td>
<td>b, c</td>
<td></td>
</tr>
<tr>
<td>Improvement in hepatocyte ballooning</td>
<td>b</td>
<td></td>
</tr>
<tr>
<td>Improvements in steatosis</td>
<td>d</td>
<td></td>
</tr>
<tr>
<td>Improvement in lobular inflammation</td>
<td>a, d</td>
<td></td>
</tr>
</tbody>
</table>

**Patients**

N=2,400  
Biopsy-confirmed NASH  
Primarily F2/F3  
F1 (≤10%) also evaluated

**Interventions**

- Obeticholic acid  
  10 mg QD
- Obeticholic acid  
  25 mg QD
- Placebo QD  
  (n=92)

**Outcomes**

**Primary:** improvement in fibrosis (with no worsening of NASH) or resolution of NASH\(^a\) (with no worsening of fibrosis) at 18 months  
**Secondary:** time to event analysis of composite outcome events at study end

---

\(^a\)P≤0.001; ^b\,P<0.05; ^c\,Resolution of NASH defined as not NAFLD or NAFLD but not NASH; ^d\,P<0.01; N=219 adult patients with biopsy-confirmed NASH or borderline NASH and histological NAS of ≥4 were randomized to receive oral obeticholic acid 25 mg once daily or placebo for 72 weeks.  
NASH, non-alcoholic steatohepatitis; QD, once daily  
Obeticholic Acid: REGENERATE Press Release

Adverse events were generally mild to moderate in severity and the most common were consistent with the known profile of OCA.

- The frequency of serious adverse events was similar across treatment arms (11% in placebo, 11% in OCA 10 mg and 14% in OCA 25 mg) and no SAE occurred in >1% in any treatment arm.
- There were 3 deaths in the study (2 in placebo: bone cancer and cardiac arrest, 1 in OCA 25 mg: glioblastoma) and none were considered related to treatment.
- The most common adverse event reported was dose-related pruritus (19% in placebo, 28% in OCA 10 mg and 51% in OCA 25 mg). The large majority of pruritus events were mild to moderate, with severe pruritus occurring in a small number of patients (<1% in placebo, <1% in OCA 10 mg and 5%) in OCA 25 mg).
- A higher incidence of pruritus associated treatment discontinuation was observed for OCA 25 mg (<1% in placebo, <1% in OCA 10 mg and 9% in OCA 25 mg). According to the clinical study protocol, investigator assessed severe pruritus mandated treatment discontinuation.
- Consistent with observations from previous NASH studies, OCA treatment was associated with an increase in LDL cholesterol, with a peak increase of 22.6 mg/dL at 4 weeks and subsequently reversing and approaching baseline at month 18 (4.0 mg/dL increase from baseline). Triglycerides rapidly and continually decreased in the OCA treatment arms through month 18.
- There were few and varied serious cardiovascular events and incidence was balanced across the three treatment arms (2% in placebo, 1% in OCA 10 mg and 2% in OCA 25 mg).
- With respect to hepatobiliary events, more patients (3%) on OCA 25 mg experienced gallstones or cholecystitis compared to <1% on placebo and 1% on OCA 10 mg.
- While numerically higher in the OCA 25 mg treatment arm, serious hepatic adverse events were uncommon with <1% incidence in each of the three treatment arms.

Selonsertib: Phase 2 and 3 Clinical Trials

Fibrosis Improvement (≥1 stage from baseline)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Subjects, %</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selonsertib 18 mg±SIM</td>
<td>43</td>
<td>1 stage</td>
</tr>
<tr>
<td>Selonsertib 6 mg±SIM</td>
<td>30</td>
<td>1 stage</td>
</tr>
<tr>
<td>Simtuzumab</td>
<td>20</td>
<td>1 stage</td>
</tr>
</tbody>
</table>

Progression to Cirrhosis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Subjects, %</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selonsertib 18 mg±SIM</td>
<td>3</td>
<td>1 stage</td>
</tr>
<tr>
<td>Selonsertib 6 mg±SIM</td>
<td>7</td>
<td>1 stage</td>
</tr>
<tr>
<td>Simtuzumab</td>
<td>20</td>
<td>1 stage</td>
</tr>
</tbody>
</table>

STELLAR-4 Press Release:
“In the study of 877 enrolled patients who received study drug, **14.4 percent of patients** treated with selonsertib 18 mg (p=0.56 vs. placebo) and **12.5 percent of patients** treated with selonsertib 6 mg (p=1.00) achieved a ≥ 1-stage improvement in fibrosis according to the NASH Clinical Research Network (CRN) classification without worsening of NASH after 48 weeks of treatment, compared with **12.8 percent of patients** who received placebo. Selonsertib was generally well-tolerated and safety results were consistent with prior studies.”

<table>
<thead>
<tr>
<th>Insulin Sensitivity</th>
<th>Hepatic Fibrosis and Inflammation</th>
<th>Hepatic Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
<td><strong>Proposed mechanism of action</strong></td>
<td><strong>Agent</strong></td>
</tr>
<tr>
<td>Lanifibranor</td>
<td>Improved lipid/glucose metabolism; anti-inflammatory (PPAR α/δ pathways)</td>
<td>Emricasan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prevention of caspase activation and apoptosis (caspase inhibitor)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhibition of fibrosis pathways (Galectin-3 inhibitor)</td>
</tr>
<tr>
<td>MSDC-0602K</td>
<td>Mitochondrial metabolism and FA oxidation (mTOT activator)</td>
<td>GR-MD-02</td>
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<tr>
<td>Saroglitazar</td>
<td>Improved lipid/glucose metabolism; anti-inflammatory (PPAR α/γ pathways)</td>
<td>EDP 305</td>
</tr>
<tr>
<td></td>
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<td>Regulation of hepatic glucose/lipid metabolism (FXR agonist)</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>Improved lipid/glucose metabolism; weight loss (GLP-1RA)</td>
<td>GS 9674</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Regulation of hepatic glucose/lipid metabolism (FXR agonist)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhibition of hepatic de novo lipogenesis (ACC inhibitor)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amine oxidase/RNAi inhibitor (VAP-1 inhibitor)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduction of hepatic de novo lipogenesis (THR β-selective agonist)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduction of hepatic de novo lipogenesis (THR β-selective agonist)</td>
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<tr>
<td>Tropifexor</td>
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<td>Regulation of hepatic glucose/lipid metabolism (FXR agonist)</td>
</tr>
<tr>
<td>Volixbat</td>
<td></td>
<td>Inhibition of bile uptake (IBAT inhibitor)</td>
</tr>
<tr>
<td>Simtuzumab</td>
<td></td>
<td>Inhibit fibrogenesis by preventing collagen cross-linkage (anti-LOXL2)</td>
</tr>
</tbody>
</table>
Current Management of NASH
Liraglutide (GLP-1 Agonists): LEAN

*P≤0.05

Longitudinal Pattern of Weight Loss with GLP1 Agonists

83% of patients had weight loss ≥5%
Effect of semaglutide on liver enzymes in subjects with obesity and elevated ALT: Data from a randomized Phase 2 trial

- Semaglutide improves ALT
  - Improvement seems to be associated with weight loss
  - Histology based studies are ongoing
- GLP-1RAs-AASLD 2018
  - It is premature to consider GLP-1 agonists to specifically treat liver disease in patients with NAFLD or NASH
# Targeting Multiple Pathways

## Combinations with Complementary Mechanisms of Action

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Disease Process/Pathway Target(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASK1 inhibitor (selonsertib) and non-steroidal FXR agonist (GS-9674) and/or ACC inhibitor (GS-0976)</td>
<td>Inflammation, fibrosis, and lipogenesis</td>
</tr>
<tr>
<td>Combined PPAR alpha and delta agonist (elafibranor) and an FXR agonist</td>
<td>Inflammation, fibrosis, and lipogenesis</td>
</tr>
<tr>
<td>Chemokine CCR2/CCR5 receptor blocker (cenicriviroc) in combination with a FXR agonist</td>
<td>Inflammatory and fibrosis</td>
</tr>
</tbody>
</table>

Combination of an apoptosis signal-regulating kinase (ASK1) inhibitor (selonsertib) with an acetyl-CoA carboxylase inhibitor (GS-0976) or a farnesoid X receptor agonist (GS-9674) in NASH

![Graph showing relative change in MRI-PDFF](image)

<table>
<thead>
<tr>
<th>≥30% relative reduction</th>
<th>10% (1/10)</th>
<th>70% (7/10)</th>
<th>0% (0/10)</th>
<th>50% (10/20)</th>
<th>15% (3/20)</th>
</tr>
</thead>
</table>

ACC, acetyl-CoA carboxylase; ASK-1, apoptosis signal-regulating kinase 1; CCR, chemokine (C-C motif) receptor; FXR, farnesoid X receptor; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NASH, non-alcoholic steatohepatitis; PPAR, peroxisome proliferator-activated receptor; SEL, selonsertib

**Physical activity**
- Aerobic & Resistance activity independently:
  - Reduce liver fat but no evidence for NASH and fibrosis

**Dietary composition**
- Modifications of diet without weight loss
  - Reduce liver fat but no evidence for NASH and fibrosis

**Weight reduction**
- Consistently beneficial
  - Steatosis ≥ 5%
  - NASH ≥ 7%
  - Fibrosis ≥ 10%

**Current Medications**
- Vitamin E and pioglitazone
- Clinical trials

**How long to treat?**
- Long term
- Multidisciplinary team
The Expanding World of Fatty Liver Disease

- NAFLD is the liver complications of obesity and is growing in all regions of the world
- NASH is the progressive form of NAFLD with increasing clinical burden
- NASH in the setting of components of MS can be more progressive
- Patients with NASH and fibrosis are the most urgent need to treatment
- Although liver biopsy is the gold standard to diagnose NASH, a number of non-invasive tests are being developed
- Prevention of NAFLD must parallel the public health efforts to deal with epidemic of obesity and DM
- Current SOC treatment for NASH options are limited
- A large number of potential agents are in clinical trials
- The future treatment of NASH will be similar to treatment of T2DM.
- For those with NASH and advanced fibrosis, induction followed by maintenance therapy may be required