NASH Now: Therapeutic Targets & the Competitive Clinical Trial Landscape

3rd Annual NASH Summit Europe—London, UK
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Disclosures

• Adjunct Professor of Medicine, University of Pennsylvania
• Consultant and acting Chief Medical Officer for Morphic Therapeutic (August 2018 to present)
Foundation of Lifestyle Management for NASH: Weight Loss Pyramid

Weight loss benefits steatosis, ballooning/inflammation, NASH resolution, & fibrosis

Patients achieving:
- <10% in 1 year
- 18% in 1 year
- 30% in 1 year

Patients achieving:
- ≥ 10% Weight Loss
- ≥ 7% Weight Loss
- ≥ 5% Weight Loss
- ≥ 3% Weight Loss

Adapted from Dr. Stephen Harrison’s EASL2019 Presentation
## Currently Available Drugs for Treatment of NASH

### Targeting insulin resistance

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mechanism of action</th>
<th>Trial</th>
<th>Primary endpoint(s)</th>
<th>AASLD recommendation as NASH treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Multiple</td>
<td>Multiple studies</td>
<td>Various</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>PPARγ agonist</td>
<td>PIVENS* Multiple studies</td>
<td>Improvement in NAS ≥ 2 without fibrosis worsening</td>
<td>May be used in patients with biopsy-proven NASH</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>GLP-1 receptor agonist</td>
<td>LEAN*</td>
<td>Resolution of NASH without fibrosis worsening</td>
<td>Premature to consider GLP-1 receptor agonists</td>
</tr>
</tbody>
</table>

### Targeting Oxidative stress

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mechanism of action</th>
<th>Trial</th>
<th>Primary endpoint(s)</th>
<th>AASLD recommendation as NASH treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E</td>
<td>Antioxidant</td>
<td>PIVENS*</td>
<td>Improvement in NAS ≥ 2 without fibrosis worsening</td>
<td>May be used in non-diabetic adults with biopsy-proven NASH</td>
</tr>
</tbody>
</table>

*Adapted from Dr. Stephen Harrison’s EASL2019 Presentation*
**GLP-1 Agonist Therapy in NASH: LEAN Trial (Liraglutide; Novo Nordisk)**

- Multiple GLP-1 agonism that are either on the market or in clinical development; few are being investigated in NASH
- Semaglutide: focus of Novo Nordisk NASH development
  - NCT02970942 “Investigation of Efficacy and Safety of Three Dose Levels of Subcutaneous Semaglutide Once Daily Versus Placebo in Subjects With Non-alcoholic Steatohepatitis” NASH (fibrosis stage 1, 2, 3), 320 subjects; 4 arms; Primary: NASH resolution [72 weeks]; 11/2019
  - NCT03987451 “A Research Study on How Semaglutide Works in People With Fatty Liver Disease and Liver Damage” NASH compensated cirrhosis; 69 subjects, 2 arms; Primary: MRE; 12/2020
  - NCT03987074 “Safety, Tolerability, and Efficacy of Monotherapy and Combination Regimens in Adults With Nonalcoholic Steatohepatitis (NASH)” NASH stage 2,3 fibrosis; 100 subjects; Sema + Fircocostat, Sema + Cilofexor, Sema + Firsocostat + Cilofexor; Primary safety; 6/2020

- GIP/GLP-1 agonists
- Glucagon/GLP-1 agonists

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Categorization of NASH Development Assets

**Targeted Metabolic**
- Insulin sensitizers (GLP-1)
- FGF21/19
- SGLT-1 inhibitors
- KHK inhibitor
- PUFAs
- IBAT inhibitors
- DGAT-2 inhibitors

**ROS stress reduction**
- Vitamin E
- mTOT inhibitors

**Anti-Steatosis**
- ACC inhibitors
- SCD1 inhibitors
- FASN inhibitors
- Omega-3 fatty acid

**Multifactorial Metabolic**
- PPAR agonists
- FXR agonists
- THRβ agonists
- LXR agonists
- Mito pyruvate carrier modulators

**Intestinal permeability**
- Larazotide
- Lubiprostone

**Anti-Inflammatory/Fibrotic**
- CCR2/5 inhibitor
- ASK-1 inhibitors
- Caspase inhibitors
- Galectin-3 inhibitors
- 5-lipogenase inhibitors
- CB1 inhibitors
- A3AR antagonists
- LOXL2 inhibitors
- NOX1/4 inhibitors
- ROCK2 inhibitors
- αvβ6/1 integrin inhibitors

**Nuclear Hormone Receptors**
- Obesity
- ↑ lipids
- Metabolic Syndrome
- T2D

**Insulin Resistance**
The Critical Cirrhosis Transition: Regulatory Endpoints for Pre-Cirrhotic NASH

<table>
<thead>
<tr>
<th>Pre-cirrhotic NASH Endpoints</th>
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</thead>
<tbody>
<tr>
<td><strong>Surrogates for Accelerated Approval (agreement with Agencies as part of Phase 3 clinical trials)</strong></td>
</tr>
<tr>
<td><strong>Fibrosis:</strong> Proportion of patients who achieve ≥ 1 stage improvement in fibrosis without worsening of NASH</td>
</tr>
<tr>
<td><strong>Resolution:</strong> Proportion of patients who achieve NASH resolution without worsening of liver fibrosis</td>
</tr>
</tbody>
</table>

**FDA:** Fibrosis OR Resolution  
**EMA:** Fibrosis And Resolution
## Advanced Phase Monotherapy Programs in Pre-Cirrhotic NASH

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
</table>

### Phase 3 initiated/completed/posted
- Obeticholic Acid (FXR agonist)
- Elafibranor (PPAR α/δ)
- Resmetrion (THRβ agonist)
- Cenicriviroc (CCR2/5 inhibitor)
- Aramchol (SCD-1 inhibitor)
- MSDC-0602K (mito pyruvate carrier modulator)
- Selonsertib (ASK-1 inhibitor)**

### Phase 2 initiated/completed/posted
- Tropifexor/cilofexor/Nidufexor/EDP-305* (FXRs)
- Seladelpar (PPAR δ)*/Lanifibranor (PPAR α/δ/γ)/PXL770 (deut pio)/Saroglitazar (PPARα/γ)
- VK2809 (THRβ agonist)
- Semaglutide (GLP-1 agonist)
- MED10382 (GLP-1/glucagon agonist)
- Firsocostat/PF-05221304 (ACC inhibitor)
- NGM 282 (FGF19 agonist)
- NGM 313 (KLB receptor agonist)
- Pegbelfermin (FGF21 agonist)
  - BIO89-100, AKR-001
  - PF-06835919 (KHK inhibitor)
  - Eloibixibat (IBAT inhibitor)

### Phase 1 initiated/completed/posted
- Namodenoson (A3 adenosine receptor agonist)
- IMM-124-E (bovine colostrum)
- CORT118335 (Glucocorticoid Receptor Modulators)
- Licoglifozin (SGLT2 inhibitor)
- Icosabutate (SCFA)
- AZD4017 (11-βhydroxysteroid dehydrogenase inh)
- CC-90001 (JNK inhibitor)
- TVB-2640 (fatty acid synthase inhibitor)
- ISIS 703802 (ANGPTL3 antisense)
- AZD4076 (microRNA-103/107)
- Emricasan (Caspase inhibitor)*
- Simtuzumab (LOXL-2 inhibitor)*

* Failed primary endpoint in phase 2 trial
** Failed primary endpoint in phase 3 trial

Combination therapies covered by other speakers during Summit
# Phase 3 Clinical Trials in Pre-Cirrhotic NASH*

<table>
<thead>
<tr>
<th>Drug (Company)</th>
<th>MOA</th>
<th>Phase</th>
<th>Study Description</th>
<th>Data (estimate)</th>
</tr>
</thead>
</table>
| Obeticholic acid ( Intercept) | FXR Agonist              | 3     | REGENERATE: NASH with F2/F3 fib
Endpoint: Fibrosis OR Resolution; Composite outcomes                                      | Hit primary; NDA submitted       |
| Elafibranor (Genfit)    | PPAR α/δ agonist         | 3     | RESOLVE-IT: NASH with F1-3 fibrosis (n=2000)
Endpoints: Resolution [72 wks]; Composite outcomes                                      | Recruit complete Dec 2021        |
| Resmetriom (Madrigal)    | THR β agonist            | 3     | MAESTRO-NASH: NASH with F2-3 fibrosis (n=2000)
Endpoint: Resolution [52 wks]; Composite outcomes                                      | Recruiting June 2021             |
| Cenicriviroc (Allergan) | CCR2/5 inhibitor         | 3     | AURORA: NASH with F2-3 fibrosis (n=2000)
Endpoints: Fibrosis [12 months]; Composite outcomes                                      | Recruiting Oct 2021              |
| Aramchol (Galmed)       | SCD1 inhibitor           | 3     | ARMOR: NASH with F2/F3 fib (n~2000)
Endpoint: Fibrosis OR Resolution [52 wks]; Composite outcomes                          | Recruiting June 2022             |
| MSDC-0602K (Cirius)     | Mitochondrial
pyruvate carrier modulator | 3     | NASH with fibrosis (n=3600)
Endpoint: HbA1c [6 mo] and Resolution [12 mo]
Composite hepatic and cardiac outcomes [31 mo]                                            | Not yet recruiting December 2021 |
| Selonsertib (Gilead)    | ASK-1 inhibitor          | 3     | STELLAR-3: NASH with F3 fibrosis
Endpoints: Fibrosis; Composite outcomes                                                  | Failed primary Terminated**      |

* Includes trials that have been initiated and have information on trial posted on clinicaltrials.gov

** Continuing evaluation in combination clinical trial (ATLAS; NCT03449446)
Fibrosis improvement by ≥1 stage with no worsening of NASH (month 18 interim primary endpoint; ITT; n=931)

FXR agonist, modified bile acid

Regenerate Trial
- First positive phase 3 clinical trial in patients with NASH, fibrosis stage 2-3
- Magnitude of effect generally in line with expectations from phase 2 trial
- Secondary analyses all consistent with effect on fibrosis
- Resolution of NASH did not reach significance, but indication of effect
- LDLc & cholesterol increased, but returned to baseline by end of treatment
- AEs consistent with known OCA profile; 9% discontinued in 25mg OCA group due to pruritis; SAEs similar between groups
- NDA submitted

Data from EASL Presentation April 2019
GOLDEN-505 phase 2 trial was basis for phase 3*

- No difference using protocol-defined primary endpoint
- There was significant difference between placebo and 120 mg elafibranor with new, more stringent, modified definition of NASH reversal
- Improvement in lipid parameters and glycemic control
- Safe and well tolerated

### Table 3. Response Rate and Main Analyses for the Modified Definition of Response in Patients With bNAS ≥4 and Various Stages of Fibrosis at Baseline

<table>
<thead>
<tr>
<th>Treatment arm, n (%)</th>
<th>Placebo 80 mg</th>
<th>Elafibranor 80 mg</th>
<th>Elafibranor 120 mg</th>
<th>OR (95% CI)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All NAS ≥4</td>
<td>234 (9)</td>
<td>76 (29)</td>
<td>83 (13)</td>
<td>75 (19)</td>
<td>3.52 (1.32–9.40)</td>
</tr>
<tr>
<td>NAS ≥4 with fibrosis (any stage)</td>
<td>204 (29)</td>
<td>63 (11)</td>
<td>72 (15)</td>
<td>67 (21)</td>
<td>2.26 (1.17–9.02)</td>
</tr>
<tr>
<td>NAS ≥4 with moderate/advanced fibrosis (F2, F3)</td>
<td>118 (9)</td>
<td>41 (7)</td>
<td>39 (10)</td>
<td>38 (13)</td>
<td>18.46 (4.80–70.36)</td>
</tr>
</tbody>
</table>

*new patients, direct treatment effect.

<table>
<thead>
<tr>
<th>All patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with end of trial liver biopsy.</td>
</tr>
</tbody>
</table>

* Ratziu, et al. Gastroenterology 2016;150:1147-1159

PPARαδ agonist

RESOLVE-IT Phase 3 Trial

- Biopsy proven NASH with score of at least 1 in each component and NAS ≥4 and fibrosis scores of 1-3
- N=2000
- Placebo vs. elafibranor 120 mg daily
- Interim subpart H endpoint: Resolution of NASH at 72 weeks
- Clinical outcome composite ~4 years
- Anticipated interim results Q1 2020
**Resmetriom (MDL-3196) in Pre-Cirrhotic NASH (Madrigal)**

**Phase 2 trial was basis for phase 3 (stage 2,3 fibrosis; 36 weeks)**

- **Thyroid hormone receptor β agonist**

**MAESTRO-NASH Phase 3 Trial**
- NASH with fibrosis stage 1a, 1b, 2, 3 with NAS \( \geq 4 \) and score of at least 1 in all 3 components
- N=2000
- Placebo vs. resmetriom 80-100 mg daily
- Interim subpart H endpoint: NASH resolution with at least 2-point reduction in NAS and no worsening of fibrosis at week 52
- Clinical outcome composite (up to 54 months)
- Anticipated interim data on 900 patients Q2 2021

Data taken from NASH-Tag 2019 Presentation
Cenicriviroc in Pre-Cirrhotic NASH (Allergan)

**CENTAUR phase 2 trial was basis for phase 3**
- Analysis after 1 year of therapy

**CCR2/CCR5 inhibitor**

**AURORA Phase 3 Trial**
- NASH with fibrosis stage 2-3
- N=2000
- Placebo vs. cenicriviroc 150 mg daily
- Interim subpart H endpoint: Fibrosis reduction at 12 months
- Clinical outcome composite ~5 years
- Anticipated interim October 2021

- Analysis of the data after 2 years of treatment was not as strong
- The difference between placebo and treated was not different on the endpoint of a one stage reduction in fibrosis at 2 years

Aramchol in Pre-Cirrhotic NASH (Galmed)

ARREST phase 2 trial was basis for phase 3
- Significant reduction in HbA1c, AST, and ALT
- Numerical, non-significant reduction in progression to cirrhosis with high dose

Stearoyl-CoA desaturase (SCD-1) inhibitor
- Fatty acid bile acid conjugate
- Pre-clinical
  - Reduction in liver fat
  - Decrease fibrosis with effect on HSC’s

ARMOR Phase 3 Trial
- NASH with NAS of ≥4 with ≥1 in each component
- Fibrosis stage 2-3
- N=2000
- Placebo vs. Aramchol 300 mg BID
- Interim subpart H endpoint: Fibrosis reduction or Resolution [52 weeks]
- Clinical outcome composite ~5 years
- Anticipated interim June 2022

NASH Summit Presentation 2019
EMMINENCE phase 2 trial was basis for phase 3
- 12-month, 4 arm study in 402 subjects with NASH with NAS of ≥4 with ≥1 in each component and fibrosis stages 1-3
- Interim analysis showed statistically significant reductions in ALT and AST, measured from baseline at six months
- Statistically significant reductions in HbA1c and other measures of glycemic control and insulin resistance were observed
- Adverse event rate was similar across placebo and all doses

Mitochondrial pyruvate carrier modifier
- 2nd generation thiazolidinedione designed to modulate entry of pyruvate into mitochondria.
- Minimal direct agonism of PPARγ
- ↓ insulin resistance, ↓ de novo lipid synthesis, ↑ fatty acid oxidation and ↓ inflammation

Phase 3 Trial
- NASH with fibrosis; HbA1c >6%
- N=3600
- Placebo vs. 1 dose MSDC-0602K QD
- Primary:
  - Δ HbA1c in first 800 subjects [6 mo]
  - NASH Resolution first 1000 [12 mo]
- Secondary
  - Death, Hepatic or Cardiac events [31 mo]
- Not yet recruiting
- Anticipated primary December 2021
Fibrosis Continues to Accumulate in Cirrhosis and Distorts Liver Architecture

**Amount of Fibrosis Covers Broad Range***

**Distorted Architecture in Cirrhosis**

*Cirrhosis causes portal hypertension by increasing resistance to blood flow*
- Structural Components
- Non-structural Components

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* Data from Goodman, Harrison, and Traber

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## FDA Draft Guidance on Endpoints for Compensated NASH Cirrhosis*

<table>
<thead>
<tr>
<th>Surrogates for Accelerated Approval</th>
<th>Traditional Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA does not currently recognize any surrogate endpoints for accelerated approval under subpart H.</td>
<td>Endpoint: Effect of the investigational drug relative to placebo on the <em>composite endpoint</em> of time from randomization to the <em>first of any one</em> of the following outcome events:</td>
</tr>
<tr>
<td>Previously, the FDA did agree for phase 3 trials an endpoint of the proportion of patients who achieve ≥ 1 stage improvement in fibrosis without worsening of NASH</td>
<td>1. Complication of ascites (bacterial peritonitis, diuretic-resistant ascites, hepato-pleural effusion, etc.)</td>
</tr>
<tr>
<td>“Histological improvements in fibrosis can be proposed and justified; however, at present the relationship between histological changes in cirrhosis and clinical outcomes has not been characterized, and further, reversal of cirrhosis (e.g., fibrosis stage F4) may not be feasible. Because currently there is <em>insufficient evidence to support the use of histological improvements as a surrogate endpoint</em> that is reasonably likely to predict clinical benefit to support accelerated approval, in general, the FDA expects to evaluate drugs for the treatment of compensated NASH cirrhosis under the traditional approval pathway.”</td>
<td>2. Variceal hemorrhage</td>
</tr>
<tr>
<td></td>
<td>3. Hepatic encephalopathy</td>
</tr>
<tr>
<td></td>
<td>4. Worsening in the MELD score to ≤15 (this assumes the MELD at enrollment is ≤12)</td>
</tr>
<tr>
<td></td>
<td>5. Liver transplantation</td>
</tr>
<tr>
<td></td>
<td>6. Death from any cause</td>
</tr>
</tbody>
</table>

*Nonalcoholic Steatohepatitis with Compensated Cirrhosis: Developing Drugs for Treatment, Guidance for Industry, U.S. FDA, June 2019

Timeframe for comments on the draft guidance closed in August 2019

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NASH Cirrhosis-Related Mortality Increases with Decompensation Events

↑ Liver Fibrosis

Chronic Liver Disease → Compensated Cirrhosis → Decompensated Cirrhosis

- Variceal Bleeding
- Ascites
- Encephalopathy
- Jaundice/Liver Failure
- Hepatocellular Carcinoma

D’Aminco et. Al., J Hepatol 2006;44:217 (Graphic borrowed from Dr. Guadalupe Garcia-Tso)

Median survival >12 yrs
Median survival ~ 2 yrs
Categorization of NASH Development Assets (Those Used in Cirrhosis Highlighted)

**Targeted Metabolic**
- Insulin sensitizers (GLP-1)
  - FGF21/19
  - SGLT-1 inhibitors
- KHK inhibitor
- PUFAs
- IBAT inhibitors
- DGAT-2 inhibitors

**ROS stress reduction**
- Vitamin E
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**Anti-Steatosis**
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- Omega-3 fatty acid

**Multifactorial Metabolic**
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**Anti-Inflammatory/Fibrotic**
- CCR2/5 inhibitor
- ASK-1 inhibitors
- Caspase inhibitors
- Galectin-3 inhibitors
- 5-lipogenase inhibitors
- CB1 inhibitors
- A3AR antagonists
- LOXL2 inhibitors

Modified/Expanded from EASL2019 Phenex Presentation
Advanced Phase (2 & 3) Monotherapy Programs in NASH Cirrhosis

- Obeticholic Acid
- Selonsertib**
- Simtuzumab*
- Emricasan*

* Failed primary endpoint in phase 2 trial
** Failed primary endpoint in phase 3 trial

Phase 3 initiated/completed/posted

- Belapectin (gal-3 inhibitor)*
- Pegbelfermin (FGF21)
Phase 3 and 2 Clinical Trials in NASH Cirrhosis Have Been Disappointing*

<table>
<thead>
<tr>
<th>Drug (Company)</th>
<th>MOA</th>
<th>Phase</th>
<th>Study Description</th>
<th>Data</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selonsertib (GILD)</td>
<td>ASK-1 inhibitor</td>
<td>3</td>
<td>STELLAR-4: Comp NASH cirrhosis EP: Fibrosis; composite outcomes</td>
<td>Failed primary</td>
<td>Also failed STELLAR3 (stage 3 NASH); ATLAS P2 combination trial ongoing</td>
</tr>
<tr>
<td>Obeticholic acid (ICPT)</td>
<td>FXR Agonist</td>
<td>3</td>
<td>REVERSE: Comp NASH cirrhosis EP: Fibrosis; composite outcomes</td>
<td>JUN 2021</td>
<td>Trial ongoing; In Aug 2019 increased patients from 540 to 900 and extended Rx 12 to 18 mo</td>
</tr>
<tr>
<td>Simtuzumab (GILD)</td>
<td>LOXL2 inhibitor</td>
<td>2</td>
<td>Comp NASH cirrhosis EP: Change in HVPG</td>
<td>Failed primary</td>
<td>Also failed in pre-cirrhotic NASH to improve fibrosis. Program discontinued</td>
</tr>
<tr>
<td>Belapectin (GALT)</td>
<td>Galectin-3 inhibitor</td>
<td>2</td>
<td>NASH-CX: Comp NASH cirrhosis EP: Change in HVPG</td>
<td>Failed primary</td>
<td>Post-hoc difference in HVPG without varices and reduced development of varices; no effect on fibrosis; P3 trial planned**</td>
</tr>
<tr>
<td>Emricasan (CNAT/Novartis)</td>
<td>Pan-caspase inhibitor</td>
<td>2</td>
<td>ENCORE-PH Change in HVPG ENCORE-LF Complications</td>
<td>Failed primary</td>
<td>Post-hoc analysis showed some effect in high HVPG sub-group; Currently not progressing</td>
</tr>
<tr>
<td>Pegbelfermin (BMS)</td>
<td>PEG-FGF21</td>
<td>2</td>
<td>Comp NASH cirrhosis EP: Fibrosis</td>
<td>JAN 2020</td>
<td>Completed trial enrollment</td>
</tr>
</tbody>
</table>

* Information on trial posted on clinicaltrials.gov or reported by company
** Not posted on clinicaltrials.gov
Why Have NASH Cirrhosis Trials Failed?

- **Mechanism of Action?**
  - Most drugs tested have anti-fibrogenic/anti-inflammatory activity. None with demonstrable pro-fibrolysis activity, although was a possible mechanism of simtuzumab.

- **Adequacy of pre-clinical data?**
  - Each of the drugs evaluated had effects on fibrosis in various rodent models of NASH and toxin-induced fibrosis. Indicates lack of good correlation of human results with animal models.

- **Correct dosing in humans?**
  - None of the drugs had adequate biomarkers of target engagement, particularly in determining pharmacodynamic activity in liver. Therefore, dose finding used indirect approaches, at best.

- **Duration of therapy?**
  - When the completed and ongoing trials were started, the conventional wisdom of opinion leaders that at least one year of therapy was required. Thus most of the trials included therapy for 1-2 years. Longer therapy may be required.

- **Is there a need to combine anti-fibrotics with therapy addressing metabolic pathogenesis of NASH?**
Can Bariatric Surgery Reverse NASH Cirrhosis?

Approaches for Targeting Fibrosis in NASH Cirrhosis

Figure from ILC-2019 Presentation by Dr. Quentin Anstee

Correct Metabolic Syndrome

Pro-fibrolytics

Anti-fibroitics

↑ ECM Degradation
- Collagenases & inhibitors
- α2-Macroglobulin
- Metalloproteinases (MMPs)
- C3M

↑ ECM Formation
- PIIINP
- Hyaluronic Acid
- Type IV collagen (75)
- TIMPs (TIMP-1, etc.)
- Pro-C3/C5
Potential Combination Approaches for Use of Anti-fibrotics in NASH Cirrhosis

Combine anti-fibrotic with an anti-NASH Drug to address the underlying pathophysiology of the disorder

<table>
<thead>
<tr>
<th>Anti-NASH Drug</th>
<th>Anti-Fibrotic</th>
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</table>
Potential for $\alpha_v\beta_6$ inhibition as Anti-fibrotic: Essential Upstream Activator of TGF-β Signaling

Provided by Drs Liangsu Wang and Min Lu, Morphic Therapeutic

Chronic Injury

$\alpha_v\beta_6$ expression

TGF-β activation

Latent TGF-β

Active TGF-β

Fibrogenesis

Pulmonary Fibrosis

Idiopathic Pulmonary Fibrosis
Interstitial Lung Disease
(Scleroderma-related, Arthritis-related)

Hepatic Fibrosis

Primary Sclerosing Cholangitis
Primary Biliary Cholangitis
Non-alcoholic Steatohepatitis
Liver Cirrhosis

Renal Fibrosis

Acute Kidney Injury
Chronic Kidney Diseases
Integrin $\alpha_v\beta_6$ in Liver Fibrosis

Provided by Drs Liangsu Wang and Min Lu, Morphic Therapeutic

- $\alpha_v\beta_6$ has been shown to promote ductular reaction (DR), fibrosis, and tumorigenesis in mice
- DR reported to be common in NASH fibrosis stage $\geq 2$ by multiple studies
- DR, especially centrilobular DR, is a feature of progressive fibrosis
- $\alpha_v\beta_6$ may play a role in perpetuating NASH fibrosis through DR

Ductular reaction seen in $\geq$ F2 and increases with stage of fibrosis

Staining for Ductular Reactions

Richardson et al. GASTROENTEROLOGY 2007;133:80–90
Summary of Drug Development in NASH

- Pre-cirrhotic NASH
  - Landscape will shift with agency evaluation and potential approval of obeticholic acid
  - Five additional promising agents in phase 3 clinical trials and many drugs in phase 2
  - Evaluations of combinations well underway and will continue to be major focus

- NASH Cirrhosis
  - Focus on compensated NASH cirrhosis with the objective of preventing decompensation events and subsequent liver transplant and liver-related mortality.
  - Results of clinical trials in NASH cirrhosis have been disappointing
  - Recent FDA guidance has indicated there are no acceptable surrogate endpoints and the traditional approval pathway must be used which is based on a composite endpoint of clinical outcomes.
  - Future investigation should focus on more specific and potent anti-fibrotics (e.g. anti-integrins), pro-fibrolytics, and combination with other drugs that affect the metabolic syndrome.
Thank You!

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