Is Histologic Fibrosis Assessment an Appropriate Endpoint / Reference Standard for Clinical Trials?

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Key Points

• Clinically meaningful outcomes, not biopsy, are the gold standard for drug efficacy in NASH

• We’re ‘yoked’ to biopsy for another ~ 5 years but not longer

• Measures of true liver functional activity are the future, alone or in combination with imaging

• Endpoints in NASH cirrhosis are more straightforward
Improvements in Histologic Features and Diagnosis Associated with Improvement in Fibrosis in Nonalcoholic Steatohepatitis – NASH CRN

How Can We Get More Information About Fibrosis from Liver Biopsies?

• Collagen proportionate area (CPA, or % hepatic collagen)
• Second harmonic generation / Histoindex / AI-based assessments/ Dual photon analysis
Hepatic Collagen Content (CPA) Predicts Clinical Disease Progression in Advanced NASH

- Progression to cirrhosis increased with higher baseline % hepatic collagen (CPA) and greater change over time, but not Ishak stage 4 vs 3
  - The optimal threshold for predict progression was 6.5% HC (sensitivity 60%, specificity 61%)

- Among cirrhotics, clinical events increased with higher baseline %CPA but not Ishak stage 6 vs 5
  - The optimal BL %HC threshold to predict clinical events was 11.0% (sensitivity 78%, specificity 45%)

- The c-statistics for baseline %CPA to predict progression were higher than Ishak in patients with bridging fibrosis and cirrhosis

- % CPA correlated with liver stiffness by MRE and Fibroscan

The Natural History of Advanced Fibrosis Due to Nonalcoholic Steatohepatitis: *Data From the Simtuzumab Trials – Bx and ELF*

The Natural History of Advanced Fibrosis Due to Nonalcoholic Steatohepatitis: Data from the Simtuzumab Trials – HVPG Data

Second Harmonic Generation Fibrosis Assessment “HistolIndex”

Still prone to sampling variability!
Second Harmonic Generation Assessment in Fibrosis

Experimental Workflow for Dual Photon Quantification of Fibrosis in NAFLD

Dual-photon imaging microscopy  |  Computerized image analysis  |  Fibrosis assessment

Incidence of Liver-related Events in Patients Stratified by (A) StrPerimeter and (B) NoLongStr

StrPerimeter = perimeter of collagen fibers

NoLongStr = no. of long collagen fibers

Second Harmonic Generation Fibrosis Assessment in Madrigal Trial – 36 Weeks of Rx

- Using SHG, MGL-3196 showed a statistically significant ≥ 1-pt reduction in fibrosis score at Week 36.
- Based on pathology score, fibrosis was reduced by ≥ 1 point in 29% of MGL-3196 treated patients vs. 23% in placebo.

Courtesy of Stephen Harrison MD. https://doi.org/10.1371/journal.pone.0199166.
Detecting Change in 6 Weeks by Corrected T1
Phase 2 NASH Study with NGM-282

Decrease in cT1 shows improvement in fibroinflammatory levels within 6 weeks

Magnetic Resonance Elastography Predicts Advanced Fibrosis in Patients with NAFLD

Lessons from Pulmonary Fibrosis

Pulmonary Function Tests Correlate with Outcomes & Response to Therapy
Quantitative Function Tests in Liver Disease

- Cholate clearance
- Indocyanine green clearance
- Methacetin clearance test
- MEGX
- Galactose elimination
- Methionine breath test
Elements of Functional Impairment – ‘DSI’ Measured by the HepQuant SHUNT Test

Courtesy of Greg Everson MD.
A dose-dependent and clinically meaningful reduction in DSI was observed for OCA 10mg and OCA 25mg.
- DSI response was greater with OCA 25mg.

Dose-dependent response in DSI was consistent with the dose-dependent improvement in fibrosis observed in REGENERATE.

Proteases Regulate All Major Biological Pathways of NASH

Synthetic Biomarker Paradigm

- Ultrasensitive
- Tailor-made
- Hundreds of choices
- Measures central biology in diseased tissue
- Enhanced specificity
- High data content
- Concentrates reporters
- Low background
- Simple collection

Protease Activity Classifiers Enable Diagnosis of NASH, Progression, and Regression in Preclinical Models

A
1. Injection of GLT probes
2. Pooled urine collection
3. Mass spec analysis
4. Classification

B
Training Set
CDAHFD
CD

Test Set
CDAHFD
HFD
CD

C
Output prob. of healthy

Train
Test

CD
CDAHFD
CD
CDAHFD
HFD

Courtesy of Glympse Bio.
Liquid Biopsy Circulating DNA

Non-tumoral Liver  HCC

JAK1 mutant  JAK1 wild-type

Courtesy of A. Villanueva.
Summary – Biomarkers in NAFLD Trials

• No biomarkers are ready as primary endpoints yet, but it will be important to validate as exploratory or secondary endpoints.

• For approval: strong correlation with fibrosis initially, then with clinical outcomes. Reproducible, scalable.

• Non-invasive tests with the most conceptual promise:
  – Functional tests- Cholate shunt, HEP-QUANT STAT.
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Yes, for now, but we will do better:

A combined imaging, outcomes and/or functional assessment will replace biopsy.