Need for Biomarker Development in Non-Alcoholic Fatty Liver Disease

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Disclosure

• Éric Lefebvre is an employee of Tobira Therapeutics, Inc.
Background

Prevalence of obesity, metabolic syndrome, and T2DM is increasing rapidly...

- The definitive diagnosis of NASH currently relies on a liver biopsy, which is not recommended for routine screening.

Non-invasive tools are urgently needed to identify patients with NAFLD and to determine which ones will require a liver biopsy.
Obesity is Rapidly Increasing Among US Adults

NASH is now the second most common indication for liver transplant

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1. CDC, Behavioral Risk Factor Surveillance System (BMI ≥30 kg/m², or about 30 lbs. overweight for 5’4” person); 2. Wong et al. 2015
Biomarkers to Foster Clinical Development

• A biomarker is defined as:

> “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”\(^1\)

• Significant advances in biomarker development have improved the diagnosis and clinical management of life-threatening diseases

Validated NALFD biomarkers are needed to identify ‘at-risk’ patients and to evaluate new NASH therapies in randomized clinical trials
NASH: Severe, Progressive Form of Fatty Liver Disease

Healthy 

NAFLD 
NAFLD + inflammation

NASH 
NAFLD + inflammation

High-risk NASH 
NAFLD + inflammation and fibrosis, T2DM, high BMI

Cirrhosis HCC 
Liver failure 
Death

86–108 m in USA\(^2,3\) 
9–15 m in USA\(^4\) 
6–10m affected\(^5\) 
At greatest risk of progression to cirrhosis or other serious liver conditions

Focus of CENTAUR\(^6\) and Phase 3 studies\(^7,8\)

Liver Biopsy: The Imperfect ‘Gold-Standard’

Sampling error

Inter-operator variability

Multiple staging systems

Low patient acceptance

High costs

Procedural risks

Long intervals between serial biopsies to monitor disease progression, in practice and in clinical trials

Simply not practical or feasible in clinical practice at a global scale
Clinical Need for Biomarkers

- Identification of patients with NAFLD
- Distinction between steatosis (NAFL) and steatohepatitis (NASH)
- Discrimination between stages of liver fibrosis (1-4)
- Sensitivity to change (progression + regression) and treatment effects
- Correlation with clinical outcomes, including cirrhosis, CVD and cancer
Criteria for an Ideal Biomarker

- Biologically plausible, accurate and reproducible
- Rapid, inexpensive, non-invasive, readily available
- Suitable for screening, diagnosis and monitoring
- Correlates with disease activity and fibrosis stage
- Capable of detecting treatment effects
- Predictive of clinical outcomes
The Molecular Engines that Drive NASH

- NAFLD
- Metabolic abnormality
- Inflammation
- NASH
- Fibrosis
- Cirrhosis HCC

Adapted from Arun Sanyal, NASH Symposium Paris June 2015
Currently Available Biomarkers

- Fatty Liver Index (FLI), Model For End-Stage Liver Disease (MELD) score, Child-Pugh score
- Steatosis/steatohepatitis: Cytokeratin-18 (CK-18) fragments (M30, M65)
- Fibrosis: FIB-4, APRI, AST/ALT ratio (AAR), Enhanced Liver Fibrosis score (ELF), NAFLD Fibrosis Score (NFS), FibroTest, HepaScore, FibroMeter
- Hepatic function
- Apoptosis: Adipose tissue insulin resistance index (Adipo-IRi), Adiponectin

References:
Biomarkers to Enrich Trials for ‘High-Risk’ Patients

- High positive predictive values of APRI and FIB-4 in CENTAUR suggest that validated scores can aid in the selection of adults with fibrotic NASH and may be used to enrich studies while reducing the number of screening liver biopsies.

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APRI and FIB-4 Index Scores Can Enrich for Subjects With Fibrotic Non-Alcoholic Steatohepatitis (NASH) in Clinical Trials - The CENTAUR Trial Data

Arun J. Sanyal, Vlad Ratziu, Zachary Goodman, Eric Lefebvre, Jeffrey Vest, Mildred D. Gotwals, Laurent Fischer, Scott L. Friedman

Background and aims: Cenicriviroc (CVC), a dual C-C chemokine receptor types 2 and 5 (CCR2/CCR5) antagonist, is an anti-inflammatory and antifibrotic agent that reduced aspartate aminotransferase-to-platelet count ratio index (APRI) and non-invasive hepatic fibrosis risk (FIB-4) score in HIV-positive subjects, with favorable tolerability in ~600 participants. CVC is currently being evaluated in a Phase 2b, randomized, double-blind, multinational, 2-year study in 289 subjects with non-alcoholic steatohepatitis (NASH) and liver fibrosis (CENTAUR; NCT02217475). An exploratory analysis was performed on screening liver biopsy results to evaluate associations between APRI/FIB-4 scores and fibrosis stage. Methods: Subjects with histological evidence of NASH (non-alcoholic fatty liver disease activity score [NAS] ≥4) and liver fibrosis (Stages 1-3 NASH Clinical Research Network [CRN] system) enrolled. Eligible subjects at increased risk of progression to cirrhosis due to presence of one or more of the following: type 2 diabetes; body mass index >25 kg/m² with ≥1 feature of metabolic syndrome; bridging fibrosis and/or NAS ≥5. Screening liver biopsy results (N=566) were analyzed, with mean APRI and FIB-4 scores and standard deviations (SD) calculated for each NASH CRN stage. Differences in means across stages were compared using contrasts.
A Wilcoxon Rank Sum analysis showed that a 10% improvement in median FIB-4 values at 24 weeks is associated with a ≥1 stage improvement in fibrosis stage at 72 weeks (p=0.0448)
Biomarkers Under Development

Circulating biomarkers
- miRNA
- Exosomes, proteomics
- Metabolomics, lipidomics
- Focused markers linked to pathophysiology

Microbiome
- Fecal
- Circulating

Quantitative
- Cholate clearance
- Methacetin breath test
**Identification of ‘High-Risk’ Patients**

**Suspected NAFLD**
(Hepatic steatosis on imaging ± elevated serum ALT)

**Low-risk profile**
- BMI <29.9
- No T2DM or metabolic syndrome features
- Non-invasive fibrosis estimation:**
  - FIB-4 <1.3
  - APRI <0.5
  - NFS < -1.455
- Fibroscan® <5 kPa*

Follow patient and reassess as risk factors evolve

**Intermediate-risk profile**
- BMI >29.9
- Multiple features of the metabolic syndrome
- Non-invasive fibrosis estimation:**
  - FIB-4 1.3–2.67
  - APRI 0.5–1.5
  - NFS -1.455–0.675
- Fibroscan® 6–11 kPa*

Consider liver biopsy

**High-risk profile**
- AST>ALT
- Platelets <150k
- Non-invasive fibrosis estimation:**
  - FIB-4 >2.67
  - APRI >1.5
  - NFS >0.675
- Fibroscan® >11 kPa*

Consider liver biopsy or confirmatory testing for cirrhosis, such as MR elastography

*High-quality data for the use of Fibroscan® (Echosens, France) in patients with NASH are emerging and require confirmation

**Cut-off values reported by Angulo et al. 2013

Biomarkers in NAFLD Therapeutics

• The investigational NASH treatment landscape is evolving

  Pivotal studies currently require a liver biopsy for determining eligibility and evaluating treatment effects

  Guidelines and regulators warrant pharmacologic intervention in patients with moderate-to-severe fibrosis, estimated to be ≈25% of those with NASH \(^1\)

  New patient-selection tools are urgently needed for enrichment strategies in randomized clinical trials

  Non-invasive biomarkers will enable diagnosis of NAFLD, improve patient management and foster clinical development of NASH therapies

Angulo et al. 2015
Call for Action

Raising awareness of NAFLD and improving diagnosis is critical

Non-invasive tests are needed for disease management and prognosis

Biomarkers must be evaluated and validated in NASH clinical trials

Collaboration between key stakeholders (e.g. The Liver Forum) on biomarker development will be essential to unlock the full potential of new NASH therapies and curb the impact of this looming health threat
Questions

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