Non-invasive tests as Diagnostic Biomarkers and Surrogate Endpoints for NASH Clinical Trials Workshop – July 11 – 12, 2023

BACKGROUND INFORMATION

FDA held the first workshop to discuss the endpoints in clinical trials for non-alcoholic steatohepatitis (NASH) in 2013. Since then, drug development for NASH with liver fibrosis has increased substantially; and there has been great interest in developing noninvasive tests (NITs) to detect the presence of fibrosis and to accurately classify stages of fibrosis as well as cirrhosis. Candidate NITs include both blood tests (circulatory biomarkers) and imaging tests.

In recent years, data regarding NIT utility have been collected from NASH clinical trials. A key limitation for widespread NIT use is that some data were collected only in a higher-risk population, i.e., mostly in patients who have NASH with stage 2 or 3 fibrosis, or in subjects with NASH-related cirrhosis. Some data in NASH with stage 1 fibrosis are also available. However, there are no published data for NITs in a NASH population without evidence of fibrosis, i.e., stage 0.

Whether the NIT thresholds selected, based on prior data from the NASH population studied in clinical trials can accurately identify patients with NASH who have fibrosis in the general population is unknown. In the general population, patients may have co-morbid diseases; whether these comorbidities influence the results obtained from NIT's are also not known.

Currently available non-invasive tests:

1. Circulatory NITs: Some of the currently available serologically based biomarkers include, (1), aspartate aminotransferase (AST) to platelet ratio (APRI); (2), FibroTest/FibroSure; (3), NIS-4; (4), FibroSpect; (5), FIB-4 score; and (5), ELF score, etc.
2. Imaging NITs that are available include elastography, liver stiffness as assessed by transient elastography (TEE), acoustic radiation force impulse (ARFI), shear wave elastography, magnetic resonance elastography **(**MRE), magnetic resonance imaging cT1, and proton density fat-fraction (MRI-PDFF).

Limitations of NITs

Limitations with all the currently available NITs is that none can be used for detecting inflammation and hepatocyte ballooning in the liver. Both inflammation and ballooning are key components for the primary efficacy assessment for drug development that are evaluated for the treatment indication of NASH. The FDA guidance allow assessment of resolution of NASH with no worsening of fibrosis, or improvement in fibrosis with no worsening of NASH.

A limitation of elastography is that the relative contributions to liver stiffness from inflammation and fibrosis cannot be separated. In theory, a patient with advanced fibrosis and minimal inflammation may have a similar "stiffness" score as a patient with more severe inflammation and mild fibrosis. Is the risk of disease progression and subsequent adverse outcomes between these two patients similar regardless of the relative contributions of inflammation and fibrosis to the elastography score?

Currently, FDA supports use of NITs for the following purposes:

1. In early drug development (phase 1 and phase 2a (proof-of-concept)) trials
    a. To assess preliminary evidence of efficacy by pharmacodynamic biomarkers and other biomarkers
    b. To screen study subjects for NASH with fibrosis
2. In phase 3 (pivotal) trials, patients are screened using NITs, so that patients at high risk for NASH with fibrosis are identified prior to obtaining a liver biopsy.

Currently, FDA considers the following endpoints to be surrogate endpoints reasonably likely to predict clinical benefit which can support an accelerated approval for the marketing indication of NASH with fibrosis, as stated in the *Draft Guidance for Industry: Non-Cirrhotic, Non-Alcoholic Steatohepatitis: Developing Drugs for Treatment*[1].

1. Resolution of NASH[2] with no worsening of fibrosis
2. One stage improvement in fibrosis with no worsening of NASH[3]
3. Or meeting #1 and #2 as co-primary endpoints

Clinical investigators and industry have proposed using NITs as surrogate endpoints i.e., "that are reasonably likely to predict clinical benefit" for assessing the primary efficacy of drugs to support approval via accelerated approval pathway for treatment of NASH with fibrosis. However, data to support use of NITs as reasonably likely to predict surrogates are limited and at present may not be ready to replace histological assessment to gauge efficacy.

[1] Noncirrhotic Nonalcoholic Steatohepatitis with Liver Fibrosis: Developing Drugs for Treatment Guidance for Industry.
[2] Resolution of NASH defined as NAS score of 0–1 for inflammation, 0 for ballooning, and any value for steatosis
[3] No worsening of NASH defined as no worsening in NAS for ballooning, inflammation, or steatosis