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MRI-Proton Density Fat Fraction Treatment Response Criteria in Nonalcoholic Steatohepatitis

NASH is one of leading causes of chronic liver disease in the United States.[1] NASH can lead to cirrhosis, end-stage liver disease, and hepatocellular carcinoma and has become one of the leading indications for liver transplant in the United States.[2] Reversal of NASH and improvement of NASH-related fibrosis is a major unmet need in the field of liver disease. Several therapies have shown promise in the treatment of NASH-related fibrosis, but there are no US Food and Drug Administration (FDA)-approved or European Medicines Agency (EMA)-approved therapies.

Over the past 10 years, there has been a tremendous increase in the number of agents being evaluated for treatment of NASH-related fibrosis. Both the FDA and EMA have provided guidance regarding regulatory approval for drugs used in the treatment of NASH-related fibrosis. The acceptable endpoints for full approval include progression to cirrhosis, clinical hepatic decompensation, and a MELD score ≥15. However, because of the long natural history of NASH-related fibrosis, a subpart H pathway is provided to show improvement in liver histology as a surrogate endpoint for interim approval while data are being collected for long-term clinical outcomes. These histologic endpoints include ≥1 stage improvement in fibrosis without worsening of NASH and/or resolution of NASH without worsening of fibrosis.

Histologic endpoints, although useful, pose significant limitations to clinical drug development in NASH. These limitations include the invasive nature of the liver biopsy assessment, subjective assessment of histology, low intrareader and inter-rater reliability, lack of precision and reproducibility, and long duration required to show a treatment benefit. Therefore, there is a need for a precise, reproducible, accurate biomarker for treatment response, especially in early Phase 1 and 2A trials in which histologic response assessment is impractical and may increase the risk of type 2 errors, i.e., declaring a therapy to be ineffective although it may improve NASH-related fibrosis in a larger and longer trial.[3]

Over the last 10 years, many noninvasive tests, both serum and imaging-based biomarkers, have been proposed to assess treatment response in NASH.[4] Among the cadre of these noninvasive biomarkers, MRI-proton density fat fraction (MRI-PDFF) is one of the leading imaging-based biomarkers of assessing antisteatotic benefits of a drug therapy in NASH.[5]

Abbreviations: NAS, NAFLD activity score; MRI-PDFF, MRI-proton density fat fraction.

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MRI-PDFF is a precise, reproducible, and accurate imaging-based biomarker of liver fat quantification.[3] MRI-PDFF cannot be performed in patients who have contraindications for getting an MRI, including metallic implants and severe claustrophobia. Furthermore, it is expensive and not available as a point-of-care test. MRI-PDFF has been increasingly utilized over the last 10 years for assessment of treatment response in early-phase clinical trials.[5]

Because of its increased utilization in NASH clinical trials, there is a need for standardization of criteria for assessing treatment response in NASH trials. The entry criteria for MRI-PDFF typically includes a baseline MRI-PDFF ≥ 8%. In a seminal single center study, it was noted that a significant reduction in liver fat by MRI-PDFF is associated with a higher odds of ≥2 point improvement in NAFLD activity score (NAS).[6] NAS ranges from 0 to 8 and is a summary score including steatosis ranging from 0 to 3, lobular inflammation 0 to 2, and ballooning 0 to 2. In subsequent multicenter studies with diverse therapies such as selonsertib (ASK-1 inhibitor) and obeticholic acid (farnesoid X receptor agonist), these data were then validated.[7,8] The optimal cut-point that was associated with histologic response was noted to be ≥30% relative reduction in MRI-PDFF.[8] Subsequently, a recent meta-analysis has been published that provides pooled estimates on the association between MRI-PDFF responders, defined as ≥30% reduction in MRI-PDFF relative to baseline and histologic response.[9] Seven studies were examined in this meta-analysis, including 346 subjects.

TABLE 1. MRI-PDFF Treatment Response Criteria

MRI-PDFF responder is defined as a ≥30% relative reduction in MRI-PDFF between baseline and end of treatment
*Super-responder on MRI-PDFF** is defined as a ≥50% relative reduction in MRI-PDFF between baseline and end of treatment. This is associated with significantly higher rates of NASH resolution.
Primary endpoint in early phase trial when appropriate
Proportion of patients who achieved ≥30% relative reduction in MRI-PDFF between treatment versus placebo
Secondary endpoint(s)
Proportion of patients who achieved an absolute decline of ≥5% in MRI-PDFF between treatment versus placebo
Proportion of patients who achieved ≥50% relative reduction in MRI-PDFF between treatment versus placebo
Differences in mean MRI-PDFF between treatment and placebo (this may be used as a primary endpoint in Phase 1 trial for efficacy assessment given smaller sample-size of Phase 1A/B trials)

*Super-responder category data is currently in abstract or press release format only and has not been peer-reviewed.

The rate of histologic response as defined as ≥2-point improvement in NAS in MRI-PDFF responders versus nonresponders was 51% versus 14% (*P* value < 0.01), respectively, and the rate of NASH resolution as defined as 0 ballooning and 0-1 in lobular inflammation in MRI-PDFF responders versus nonresponders was 41% versus 7% (*P* value < 0.01), respectively.[9]

Compared with nonresponders, MRI-PDFF responders had significantly higher odds of ≥2-point improvement in NAS as well as NASH resolution.[9] Table 1 summarizes the MRI-PDFF response criteria that may be used for assessment of treatment response in early-phase clinical trials. A secondary analysis of the Resmetirom Trial that was presented at the Digital International Liver Meetings held in August 2020 showed that NASH resolution rate was dose-dependently higher in super-responders (MRI-PDFF ≥ 50% decline) versus responders (MRI-PDFF ≥ 30% decline) versus nonresponders (MRI-PDFF < 30% decline).[10] In this study, MRI-PDFF responders demonstrated statistically significant increased rates of ≥2 point improvement in NAS, all individual components of NAS including steatosis, lobular inflammation, and ballooning, as well as NASH resolution. Although there was a significant improvement in fibrosis, these results are preliminary and need to be validated in additional confirmatory studies. Table 1 provides data on the primary and secondary endpoints that may be used in early-phase trials. It also provides a category of super-responders on MRI-PDFF defined as those who achieve ≥50 relative reduction in MRI-PDFF.[10] The histologic response for NASH resolution was noted to be significantly higher in super-responder versus MRI-PDFF responders versus nonresponders with 64% versus 40% versus 4%, respectively.[10]

In summary, these emerging data have important implications in assessing treatment-effect delta relative to placebo in NASH trials. Understanding the quantitative association between MRI-PDFF response and degree of improvement in NAS response and NASH resolution may inform sample-size estimates for larger histology-based Phase 2b and 3 clinical trials in NASH. Hence, MRI-PDFF may be utilized for assessment of treatment response as a primary endpoint in early-phase treatment trial for therapeutic agents that have a strong antisteatotic effect and are likely to reduce liver fat content. However, MRI-PDFF may not be useful for therapeutic agents that

target primarily either inflammation or fibrosis and do not have any metabolic effects. Further research is needed to see if a combination of serum and imaging biomarkers would be able to replace the need for liver histologic assessment in Phase 3 trials.

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