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Roles of Radiological Tests in Clinical Trials and the Clinical Management of Nonalcoholic Fatty Liver Disease

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Keywords

Fibrosis; Liver biopsy; NAFLD; NASH; Ultrasound

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease worldwide.[1] The presence of fatty liver can be diagnosed by various imaging modalities or liver biopsy. Ultrasound remains the most widely used first-line tool despite its well-known limitations (low sensitivity and operator dependence). An NAFLD diagnosis requires the exclusion of excessive alcohol use, prosteatotic medications, and concurrent liver diseases. NAFLD can be classified with or without significant fibrosis and with or without substantial nonalcoholic steatohepatitis (NASH). Fibrosis is the only predictor of all-cause and liver-related mortality,[2] even after adjustment for NASH.[3,4] However, patients with NAFLD with NASH may experience more rapid fibrosis progression than patients with NAFLD without NASH[5]; therefore, clinical trial typically targets patients with NASH and stage 2 fibrosis or greater, coined as "at-risk NASH."

Although NAFLD affects a quarter of the global and US populations,[1] only 5.9% and 1.6% of the population are considered at risk for disease progression due to the presence of NASH and stages 2 and 3 fibrosis or greater, respectively.[6] Liver biopsy is the current reference standard for confirming NASH and fibrosis stage. However, the associated costs and invasive nature of liver biopsy make this procedure impractical for use in large-scale, population-based studies.[7]

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Radiological tests able to assess the stage of disease and the risk of disease progression in patients with NAFLD have been proposed for both the clinical management of NAFLD and the enrichment of candidates for clinical trials. Radiological tests include ultrasound-based tests such as vibration-controlled transient elastography (VCTE; FibroScan, Echosens, Paris, France) allowing controlled attenuation parameter (CAP) and liver stiffness measurements and magnetic resonance–based tests such as MRI-proton density fat fraction (MRI-PDFF) and magnetic resonance elastography (MRE).[8] Radiological tests can address the following: (1) quantifying liver fat for NAFLD diagnosis; (2) assessing liver fibrosis stage; and (3) evaluating longitudinal changes over time. Liver fibrosis needs to be assessed during clinical trial prescreening, as most clinical trials target populations with stage 2 fibrosis or greater, with or without an NAS of 4. Liver fibrosis is also assessed when determining whether a patient should be referred to hepatology specialists from primary care, which is recommended for patients with stage 3 fibrosis or greater or who are identified as being at risk for a liver-related outcome.

QUANTIFYING LIVER FAT FOR NONALCOHOLIC FATTY LIVER DISEASE DIAGNOSIS

Ultrasound-Based Tests

CAP, which quantifies the loss of ultrasound signal as it penetrates the liver, can be used to diagnose steatosis. Although CAP is accurate for diagnosing the presence of steatosis, it is not adequately sensitive to differentiate among different histological grades.[9,10] In a prospective study[10] of bariatric surgery patients undergoing liver biopsy comparing the diagnostic performances of CAP with MRI-PDFF, CAP had an area under the receiver operating characteristic curve (AUROC) value of 0.83 for the diagnosis of steatosis greater than 5%, but the AUROC value decreased to 0.79 and 0.73 for the diagnosis of steatosis greater than 33% and greater than 66%, respectively. In addition, CAP was outperformed by MRI-PDFF. Given the CAP's poor performance in quantifying steatosis, it may not be adequate for detecting dynamic changes in steatosis in the context of monitoring progression in clinical care or clinical trials.

The optimal cutoff value for diagnosing NAFLD varies depending on the patient population and the probe being used.[11] Two types of probes, M and XL, are available, and the device automatically recommends the use of an XL probe if the skin to liver capsule distance is greater than 25 mm. The optimal cutoff value when using the XL probe may be 10 dB/m higher than when using the M probe.[12] An individual patient data meta-analysis[13] including data for 2346 patients and using XL probe indicated that CAP results can be influenced by cause, diabetes, and body mass index. In studies of patients with NAFLD, optimal CAP cutoff values at 288 dB/m[14] and 306 dB/m[15] were proposed when using MRI-PDFF and liver biopsy as references, respectively. Finally, in the absence of consensual cutoffs, recent European Association for the Study of the Liver (EASL) guidelines[16] stated that, given their sensitivity greater than 90%, values greater than 275 dB/m could be used to diagnose NAFLD.

Magnetic Resonance–Based Tests

As MRI-PDFF is the most accurate noninvasive method to quantify steatosis,[17] it has been used in many clinical trials.[18] MR spectroscopy (MRS) is another highly accurate method for measuring steatosis[19] but is limited by costs, instrument availability, and analytical algorithms. Although the findings derived from MRI-PDFF and MRS correlate closely in clinical trials,[20] a cross-sectional study suggested that MRI-PDFF may be more accurate than MRS.

Evaluating Longitudinal Changes Over Time

Currently, MRI-PDFF is the only technique able to evaluate change in steatosis grade over time, with a reasonable AUROC of 0.70. The ability of MRI-PDFF to detect a greater than or equal to 2-point improvement in NAS or NASH resolution and the ability of MRE to measure fibrosis improvements remain suboptimal, and liver biopsies continue to be necessary to assess improvements in phase 3 clinical trials. However, the reference standard that MRI-PDFF is being compared with is liver biopsy, which is characterized by significant variability that may adversely affect the relative performance of MRI-PDFF. MRI-PDFF is currently allowed for the assessment of primary endpoints in phase 2 clinical trials when evaluating agents believed to have a strong antisteatotic effect.

In a study of selonsertib,[21] 54 patients underwent paired liver biopsies and MRE assessments performed at baseline and at week 24. Fibrosis improvement (≥1-stage reduction) was noted in 18 (33%) liver biopsy samples. The AUROC value for the ability of MRE to detect fibrosis improvement was 0.62, and the optimal threshold was a relative change of 0%. Among 65 patients with paired liver biopsies and MRI-PDFF assessments performed at baseline and at week 24, steatosis improvement (≥1-grade reduction) was noted in 18 (28%) liver biopsy samples. The AUROC value for the ability of MRI-PDFF to predict steatosis improvement was 0.70, and the optimal threshold was a relative change of 0%. In a secondary analysis of the FLINT trial,[22] paired MRI-PDFF and liver biopsies from 78 patients were compared to determine the ability of MRI-PDFF to detect a histologically determined 2-point improvement in NAS without fibrosis worsening. MRI-PDFF had an AUROC value of 0.60, using a relative improvement of 30% as the optimal cutoff value. Alternatively,[23] MRI-PDFF was able to identify a 1-grade reduction in steatosis with an AUROC value of 0.81 and a 1-grade worsening in steatosis with an AUROC value of 0.81.

In a meta-analysis of 7 clinical trials, including 346 subjects,[24] MRI-PDFF responders (relative decline of ≥30% in liver fat) were significantly more likely than nonresponders to have a greater than or equal to 2-point improvement in NAS (51% vs 14%, pooled odds ratio [OR]: 6.98) and NASH resolution (41% vs 7%, pooled OR: 5.45).

MRI-PDFF interexamination repeatability has been estimated with a standard deviation (SD) of less than 0.5%. A longitudinal hepatic change of greater than 1.8% in MRI-PDFF, which is twice the maximum aggregate (SD), represents real change rather than measurement imprecision.[25] The reduction in AUROC values observed in longitudinal studies compared with cross-sectional studies may be associated with the use of liver biopsies as the reference and the degree of variability observed in biopsy results. In the colesevelam study,[20] an

increase in hepatic steatosis compared with placebo after 24 weeks was detected by MRI-PDFF but not by liver biopsy. In 50 patients with data for longitudinal liver biopsies,[26] MRI-PDFF, MRS-PDFF, liver enzyme, and weight measurements, patients who displayed a greater than 1% increase or decrease in PDFF showed parallel increases in body weights and liver enzymes that could not be confirmed by histology. Both studies suggest that MRI-PDFF may be more sensitive than liver biopsy for determining changes in liver fat content.

ASSESSING LIVER FIBROSIS OR FIBROTIC NONALCOHOLIC STEATOHEPATITIS IN THE CONTEXT OF CLINICAL TRIAL PRESCREENING

Ultrasound-Based Tests

Advanced fibrosis—A meta-analysis of 37 primary studies including 5735 patients[27] showed that VCTE had AUROC values of 0.85 and 0.90 for diagnosing advanced stage 3 fibrosis or greater and cirrhosis. Youden index identified optimal cutoff values of 9.1 kPa for stage 3 fibrosis or greater and 10.4 kPa for cirrhosis. NASH-specific studies from NASH Clinical Research Network[9] and other pooled analysis[28] showed that VCTE had AUROC values of 0.83 to 0.84 for diagnosing advanced fibrosis and 0.84 to 0.93 for diagnosing cirrhosis. Youden index identified optimal cutoff values of 8.6 to 8.8 kPa for advanced fibrosis and 11.8 to 13.1 kPa for cirrhosis.

Many studies have explored the use of a dual-cutoff strategy with VCTE for the diagnosis of advanced fibrosis. Advanced fibrosis can be ruled out by lower cutoff values and ruled in by higher cutoff values, although patients between the 2 cutoff values will continue to require a liver biopsy to confirm fibrosis. In a meta-analysis,[27] dual cutoff values of 7.4 and 12.1 kPa were able to achieve 90% sensitivity and specificity. Using a single cutoff value of 9.1 kPa resulted in the misclassification of 22% of patients, whereas the use of dual values resulted in the misclassification of 10% of patients and the classification of 31% of patients as indeterminate.

Combining simple, noninvasive blood tests with VCTE, either simultaneously or sequentially, can improve screening accuracy. For example, various strategies have been developed for combining paired cutoff values for both the fibrosis-4 (FIB-4) and VCTE.[27,29] In this large meta-analysis in 5737 patients with NAFLD, the sequential combination of FIB-4 cutoffs (<1.3; ≥2.67) followed by VCTE cutoffs (<8.0; ≥10.0 kPa) to rule-in or rule-out advanced fibrosis had sensitivity and specificity (95% CI) of 66% (63–68) and 86% (84–87), with 33% needing a biopsy to establish a final diagnosis.

The rate at which patients are classified as indeterminate or misclassified depends on the prevalence of advanced fibrosis. In screening for the STELLAR[30] study, for which the prevalence of advanced fibrosis was as high as 70% to 80%, a simultaneous strategy may be preferred, as it lowers the misclassification rate from 20% to 5% at the cost of indeterminate rate.

Fibrotic nonalcoholic steatohepatitis—The FibroScan-aspartate aminotransferase (FAST) score (Echosens, Paris, France) has been proposed to select eligible candidates

for clinical trials, that is, patients with fibrotic NASH (stage ≥2 fibrosis with NAS ≥4).[31] It combines CAP, liver stiffness, and aspartate transaminase levels and can be calculated on a free app. It ranges from 0 to 1, with rule-out and rule-in cutoffs of 0.35 (90% sensitivity) and 0.67 (90% specificity). Its AUROC was 0.80 in the training cohort and 0.85 in the validation cohort.[27] Further independent validation[32] of the FAST score shows that this score is highly[33,34] reproducible and unaffected by differences in ultrasound equipment or probes. Limitation of the FAST score is its low positive predictive value.

Magnetic Resonance Elastography–Based Tests

Advanced fibrosis—MRE has excellent accuracy with AUROC of 0.93 for the diagnosis of advanced fibrosis (stage 3 and 4).[35] Several head-to-head comparison studies have shown that MRE outperformed VCTE in detection of fibrosis stages.[36,37] However, use of MRE in clinical practice is hampered by cost and limited availability. Thus MRE is more suited for clinical trials.[16]

MRE combined with the FIB-4 (MEFIB) was developed as a 2-step screening algorithm for clinical trial assessment at the University of California San Diego. The endpoint was stage 2 fibrosis or greater in patients with NAFLD. MRE has an AUROC value of 0.93, and FIB-4 has an AUROC value of 0.78 for the detection of fibrosis. The sequential application of the FIB-4 and MRE was proposed, in which patients with FIB-4 scores greater than or equal to 1.6 receive MRE screening at a referral center. A high positive predictive value of 95% was established for the combination of MRE greater than or equal to 3.3 kPa and FIB-4 greater than or equal to 1.6, and these patients were classified as excellent candidates for screening liver biopsies.[38]

The MEFIB strategy has been shown to be superior to FAST score[39,40] for diagnosing stage 2 fibrosis or greater alone, although FAST was originally designed to diagnose stage 2 or greater with NAS greater than or equal to 4.

Fibrotic nonalcoholic steatohepatitis—The MAST score, an MRI-serum-based score, has been recently proposed for diagnosing fibrotic NASH.[41] It combines MRI-PDFF, liver stiffness using MRE, and aspartate transaminase levels. It ranges from 0 to 1, with rule-out and rule-in cutoffs of 0.165 (90% sensitivity) and 0.242 (90% specificity). Its AUROC was 0.93 in the validation cohort, and it outperformed FAST score. When compared head-to-head with FAST and MEFIB in a US and a Japanese cohort,[40] MAST was outperformed by MEFIB in the US cohort but not in the Japanese cohort. Further studies are needed to clarify how to best use these tests in practice.

ASSESSING LIVER FIBROSIS IN THE CONTEXT OF A DECISION TREE FOR REFERRAL TO HEPATOLOGY SPECIALISTS FROM PRIMARY CARE

Ultrasound-Based Tests

Despite the high prevalence of NAFLD in primary care (25%), only a small minority (<5%) of patients with NAFLD will develop advanced liver fibrosis. The challenge is to identify these patients, who are at the greatest risk of developing complications and need to be

referred to liver clinics for specialized management.[42] Sequential algorithms using FIB-4 as the first-line test, followed, if positive (>1.3), by VCTE are the best strategy to define pathways for patients at risk of NAFLD from primary care to liver clinics.

Such strategy was implemented in patients with type 2 diabetes (T2D) seen in primary care setting in East England.[43] FIB-4 was automatically calculated, and VCTE was ordered when the FIB-4 was greater than 1.3. Referral for secondary care was implemented for VCTE greater than 8 kPa. This approach resulted in 12.4% of patients requiring VCTE, 6.4% of patients being referred, and 4.3% of patients being diagnosed with advanced fibrosis. The advanced fibrosis detection rate increased by 7-fold upon referral; however, half of patients diagnosed with advanced fibrosis presented with normal liver function tests at the time of referral.

The prognostic value of the combined FIB-4 and VCTE strategy was evaluated in a cohort study in France.[44] Patients with FIB-4 less than 1.3 or FIB-4 greater than 1.3 and VCTE less than 8 kPa are at very low risk of experiencing a liver-related event. The study recommended retesting within 3 years among patients without T2D and within 2 years in patients with T2D.

The cost-effectiveness of the FIB-4 and VCTE combination strategy has also been compared with other combination strategies.[45] The FIB-4 and VCTE combination was able to identify patients with cirrhosis with the lowest cost per person and highest diagnostic accuracy of all examined methods, followed by MEFIB.

The sequential FIB-4 and VCTE testing approach has been recommended initially by the EASL,[16] followed by American Association of Clinical Endocrinology (AACE) and American Association for the Study of Liver Disease (AASLD).[46] All these associations propose the performance of an initial screening using the FIB-4. The EASL suggests screening patients with metabolic cofactors without specifically defining which patients to apply the FIB-4 greater than 1.30 criterion for. The AACE and AASLD broadly define the high-risk NAFLD group as those with prediabetes, T2D, obesity, more than 2 cardiometabolic risk factors, steatosis on imaging, or elevated liver enzymes. VCTE is proposed for patients with FIB-4 ranging from 1.3 to 2.67. The EASL guidelines favor VCTE for patients with FIB-4 greater than 1.3, whereas the AACE and AASLD guidelines favor referral to a hepatology specialist without further testing when FIB-4 greater than 2.67.

SUMMARY

Radiological testing is now routinely used for clinical trial prescreening, diagnosis, and treatment and to determine which primary care patients should be referred to hepatology specialists. The CAP performs well in detecting fatty liver for NAFLD diagnosis but is unable to differentiate between hepatic steatosis grades and cannot be relied on to track longitudinal changes. MRI-PDFF is a better technique for evaluating longitudinal changes and is currently used as a primary endpoint in trials investigating antisteatotic properties of therapeutic agents. The probability of detecting liver fibrosis using radiological testing techniques is high when performed at referral centers for the purposes of clinical trial

prescreening, and reasonable imaging strategies include the combination of FIB-4 and VCTE, the FAST Score, MAST, and MEFIB. When assessing liver fibrosis to determine the need for referral to hepatology specialists from primary care, the probability of detecting liver fibrosis using radiological testing is low. The strategy currently recommended by the EASL, AACE, and AASLD is the sequential application of FIB-4 and VCTE, based on availability of resources and local imaging capabilities.

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CONFLICT OF INTEREST

R. Loomba serves as a consultant to Aardvark Therapeutics, Altimmune, Anylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol-Myer Squibb, CohBar, Eli Lilly, Galmed, Gilead, Glympse bio, Hightide, Inipharma, Intercept, Inventiva, Ionis, Janssen Inc., Madrigal, Metacrine, Inc., NGM Biopharmaceuticals, Novartis, Novo Nordisk, Merck, Pfizer, Sagimet, Theratechnologies, 89 bio, Terns Pharmaceuticals, and Viking Therapeutics. In addition, his institutions received research grants from Arrowhead Pharmaceuticals, Astrazeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galectin Therapeutics, Galmed Pharmaceuticals, Gilead, Intercept, Hanmi, Intercept, Inventiva, Ionis, Janssen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Novo Nordisk, Merck, Pfizer, Sonic Incytes, and Terns Pharmaceuticals. Cofounder of LipoNexus Inc. L. Castera has served as a consultant for Alexion, Echosens, Gilead, Intercept, MSD, Novo Nordisk, Pfizer, and Sagimet and has received lectures fees from Echosens, Gilead, Intercept, and Novo Nordisk.

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KEY POINTS

- The CAP performs well in detecting fatty liver for NAFLD diagnosis but is unable to differentiate between hepatic steatosis grades and cannot be relied on to track longitudinal changes.
- MRI-PDFF is a better technique for evaluating longitudinal changes and is currently used as a primary endpoint in trials investigating antisteatotic properties of therapeutic agents.
- When assessing liver fibrosis to determine the need for referral to hepatology specialists from primary care, the probability of detecting liver fibrosis using radiological testing is low.
- The probability of detecting liver fibrosis using radiological testing techniques is high when performed at referral centers for the purposes of clinical trial prescreening, and reasonable imaging strategies include the combination of FIB-4 and VCTE, the FAST Score, MAST, and MEFIB.