Imaging NITs and NASH Treatment Response: MRI-PDFF, MRE-stiffness, and cT1

Review, and gaps in knowledge

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Disclosures

Consultation:	Alimentiv, Arrowhead, Glympse, Kowa, Median, Novo Nordisk
Lab service agreements:	Alexion, AstraZeneca, Bristol-Myers Squibb, Celgene, Enanta, Galmed, Genzyme, Gilead, Guerbet, Intercept, Ionis, Janssen, NuSirt, Organovo, Pfizer, Roche, Sanofi, Shire, Synageva, Takeda
Stockholder:	Pfizer
Co-founder:	Quantix Bio

Goals for this talk

This talk will address briefly and informally current efforts to develop NASH biomarkers for treatment response

Goals:

- Provide overview of breadth and depth of approach needed to address treatment response
- Appreciate range of ideas and studies that have been published on treatment response
- Appreciate the types of gaps in knowledge that need to be addressed
- Appreciate how future work on treatment response can be leveraged by ongoing current work:
  - FDA Biomarker Qualification Program (BQP)
  - NIMBLE and LITMUS studies
  - Current industry NASH clinical trials
- Need for a working group focused on NASH treatment response

Treatment Response - Major Gaps in Knowledge

The big one: lack of non-invasive surrogate endpoints for treatment response

- Ultimately, non-invasive biomarkers based directly on clinical outcomes when that data is available and validated
- Until then, non-invasive biomarkers validated as surrogates, for surrogate histologic endpoints

Intermediate gaps

- Comprehensive ***published performance data*** and consensus to select best biomarkers to validate
- ***Randomized controlled trials*** to validate those biomarkers
- Consideration of different ***contexts of use*** and ***drug action pathways***
- Consideration of ***placebo effect***

Organized current and future efforts to address above gaps

- Industry-supported consortia (e.g., NIMBLE, LITMUS)
- NIH-sponsored clinical research networks (e.g., NASH CRN, Liver Cirrhosis Network)
- Independent working groups (e.g., through Liver Forum, AASLD, EASL)
- Coordination with the RSNA Quantitative Imaging Biomarker Alliance (QIBA)
- Biomarker validation through the FDA Biomarker Qualification Program (BQP)
- Academic-industry partnership to benefit from and leverage existing drug development clinical trial data

Treatment Response - Contexts of Use

Predicate timepoint
- Prediction of end-of-study treatment response based on ***baseline data***
- Prediction of end-of-study treatment response based on ***early post-treatment data***
- Assessment of end-of-study treatment response based on ***end-of-treatment data***

Biomarker
- Imaging alone [e.g., hepatic PDFF, MRE stiffness, cT1]
- Combinations of imaging
- Circulating biomarkers alone
- Combinations of imaging and circulating [e.g., MEFIB=f(MRE,FIB-4); MAST=f(PDFF, MRE, AST), FAST=f(LSM,CAP,AST)]

Histologic endpoint
- Steatosis, or fibrosis (or fibro-inflammation), or inflammation, or NASH (alone)
- Combinations [e.g., NAFLD Activity Score (NAS)]

Change
- Relative vs. absolute change
- *Direction* of change (improvement, worsening, no change)
- *Amount* of change

Approach

PubMed Search

- “NASH” + “Treatment Response”: yielded 107 papers
- Elimination of titles not directly relevant to this talk left 36 papers
- Selected papers for presentation to illustrate status and progress
- Information grouped and presented by category
- Only MRI biomarkers, and only published papers

FDA Biomarker Qualification Program (BQP) website search

- Located BQP applications numbered between 1 and 144
- Nine are related to NASH contexts of use

Treatment Response - PDFF and MRE

Jayakumar et al, J Hepatology (2019), PMID: 30291868

"Longitudinal correlations between MRE, MRI-PDFF, and liver histology in patients with nonalcoholic steatohepatitis: Analysis of data from a phase II trial of selonsertib"

- **Phase II trial:** Evaluation of PDFF and MRE stiffness to assess histology in patients with NASH + NAS≥5 + (F2 or F3) after 24 weeks of treatment
- Outcomes: fibrosis improvement of ≥1 stage, steatosis improvement of ≥1 grade
- MRE: AUROC to predict fibrosis improvement was 0.62 (95% CI 0.46,0.78); optimal threshold was a ≥0% relative reduction at which: sensitivity 67%, specificity 64%, PPV 48%, NPV 79%
- PDFF: AUROC to predict steatosis improvement was 0.70 (95% CI 0.57,0.83); optimal threshold was a ≥0% relative reduction at which: sensitivity 89%, specificity 47%, PPV 39%, NPV 92%
- **Conclusion:** Supports need for further evaluation of PDFF and MRE for NASH treatment response

Treatment Response - PDFF

Stine et al, Clin Gastroenterol Hepatol (2021), PMID: 32882428

"Change in MRI-PDFF and Histologic Response in Patients With Nonalcoholic Steatohepatitis: A Systematic Review and Meta-Analysis"

- **Systematic review:** Quantification of association between ≥30% PDFF reduction and histologic response in NASH (performed according to PRISMA guidelines)
- Primary outcome: histologic response, 2-point NAS improvement with ≥1-point improvement in lobular inflammation or ballooning
- Secondary outcome: NASH resolution
- 477 abstracts and titles identified; 7 finally selected
- PDFF responders more likely to have a histologic response and NASH resolution compared to non-responder:
  - *Histologic response*: 51% vs 14%, p<0.001; OR 6.98, 95% CI 2.38, 20.43, p<0.001
  - *NASH resolution*: 41% vs 7%, p<0.001; OR 5.45, 95% CI 1.53,19.46, p=0.009
- **Conclusion:** Supports treatment response assessment by PDFF in early-phase NASH clinical trials

Early Treatment Response - PDFF

Jiang et al, Radiology (2021), PMID: 34060937

"Week 4 Liver Fat Reduction on MRI as an Early Predictor of Treatment Response in Participants with Nonalcoholic Steatohepatitis"

- Phase 1b secondary analysis of MET409 (NASH treatment drug, Farnesoid X receptor agonist; n=48)
- Predictive models developed Endpoint was ≥30% relative reduction in PDFF at 12 weeks
- Drug group (n=30) compared to placebo group (n=18)
- Early treatment response of PDFF at 4 weeks predicted later treatment response at 12 weeks
- ≥19.3% relative PDFF reduction at Week 4 predicted ≥30% relative PDFF reduction at Week 12, with an AUC of 0.98 (sensitivity 89%, specificity 95%)
- **Conclusion:** Results need to be confirmed in a prospective trial

Biomarker Response - 3D MRE (mice)

Chen et al, Alcohol Clin Exp Res (2021), PMID: 34486129

"Multiparametric magnetic resonance imaging/magnetic resonance elastography assesses progression and regression of steatosis, inflammation, and fibrosis in alcohol-associated liver disease"

- **Mouse study:** Four mouse models of induced liver disease investigated; in one model mice were binge-fed on EtOH and treated with interleukin-22 to induce disease regression
- 3D MRE Biomarkers: liver stiffness, loss modulus, damping ratio
- Three-parameter model (liver stiffness, damping ratio, ALT) predicted fibrosis progression ($r=0.84$, $p<0.0001$) and regression ($r=0.79$, $p<0.0001$))
- **Conclusion:** Early preclinical 3D MRE mouse study, shows feasibility of 3D MRE to assess disease severity and monitor treatment response in ALD; may have relevance to NAFLD

Diagnostic Performance - FAST MAST, MEFIB

Kim et al, J Hepatology (2022), PMID: 35973577

"Head-to-head comparison between MEFIB, MAST, and FAST for detecting stage 2 fibrosis or higher among patients with NAFLD"

- **Prospective 2-site study:** Patients with biopsy-proven NAFLD (n=563), contemporaneous MRE, PDFF, and Fibroscan.
- Primary objective: Compare diagnostic accuracy of MEFIB, MAST, and FAST, for (F≥2)
- Secondary objective: Compare diagnostic accuracy of MEFIB, MAST, and FAST, for NAS≥4 and F≥2
- For F≥2: MEFIB outperformed MAST and FAST ($p<0.001$); AUCs for MEFIB, MAST, and FAST were 0.901 (95% CI: 0.875, 0.928), 0.770 (95% CI: 0.730, 0.810), and 0.725 (95% CI: 0.683,0.767), respectively.
- For NAS≥4: MEFIB outperformed MAST and FAST ($p<0.05$); AUCs for MEFIB, MAST, and FAST were 0.768 (95% CI: 0.728, 0.808), 0.719 (95% CI: 0.671, 0.766), and 0.687 (95% CI: 0.640, 0.733), respectively.
- **Conclusion:** MEFIB outperformed MAST and FAST for both objectives

Alphabet Soup - FAST, MAST, MEFIB

- **MEFIB:** clinical prediction rule for F≥2 fibrosis. Rule in: MRE≥3.3 kPa, FIB-4≥1.6. Rule out: MRE <3.3 kPa, FIB-4<1.6. (Jung et al, *Gut*, **2021**, PMID: 33214165)

- **MAST:** predicts [NASH + NAS≥4 + F≥2]; formula -12.17 + 7.07*log(MRE) + 0.037*PDFF + 3.55*log(AST) (Noureddin et al, *J Hepatol*, **2022**, PMID: 34798176)

- **FAST:** predicts [NASH + NAS≥4 + F≥2]; rule in: FAST≥0.67; rule out: FAST≤ 0.35; formula $e^x/(1+e^x)$ where $x = -1.65 + 1.07*\log(\text{LSM from VCTE}) + 2.66x10^{-8}*(\text{CAP}^3 \text{ from VCTE}) – 63.3*\text{AST}^{-1}$ (Newsome et al, *Lancet Gastroenterol Hepatol*, **2020**, PMID: 32027858)

Treatment Response - PDFF and cT1

Ratziu et al, J Hepatology (2022), PMID: 36334688

"Hepatic and renal improvements with FXR agonist vonafexor in individuals with suspected fibrotic NASH"

- **Phase IIa double-blinded trial:** Evaluation of changes in PDFF and cT1 in drug and placebo arms (n=120).
- Primary endpoint: absolute change in PDFF from baseline to Week 12
- Secondary endpoints: relative change in PDFF and absolute change in cT1 from baseline to Week 12
- PDFF: Absolute PDFF reduced in 12.5% of patients in placebo arm, and 50.0% and 39.3% of patients in two drug arms, respectively. Relative PDFF reduction was 10.5% (95% CI: 19.0, 2.0) in placebo arm, and 30.4% (95% CI: 39.4, 21.3) and 25.3% (95% CI: 34.3, 16.2) in the two drug arms (all $p<0.05$)
- cT1: cT1 changed by -9.9 ms (95% CI: -38.5, 18.7) in placebo group, and by -80.2 ms (95% CI: -110.8, -49.8) and -71.8 ms (95% CI: -100.4, -43.2) in the two drug arms (all $p<0.05$)
- **Conclusion**: In this double-blind phase II trial, reductions in PDFF and cT1 were greater in drug arms than in placebo arm

Leverage FDA BQP Experience

Current active NASH-related BQP applications

DDTBMQ000051	cT1	Diagnostic enrichment
DDTBMQ000084	Circulating biomarkers	Diagnostic enrichment
DDTBMQ000095	ProC3, FAST	Diagnostic enrichment
DDTBMQ000099	MRE	Diagnostic enrichment
DDTBMQ000105	AI-based pathology	Treatment response
DDTBMQ000106	ELF, cT1	Diagnostic enrichment
DDTBMQ000112	Imaging biomarkers	Diagnostic enrichment
DDTBMQ000117	AI-based pathology	Diagnostic enrichment
DDTBMQ000131	Imaging biomarkers	Early treatment response

Use methodology in FDA-accepted BQP applications to guide future methodology

- Use of thorough literature review to formulate biomarkers to validate in clinical studies
- Lower bound of 95% Confidence Intervals of sensitivity and specificity in validation testing to meet benchmark targets
- COU bleed:
  - Treatment response biomarkers can be informed by diagnostic enrichment biomarkers
  - Prognostic biomarkers can overlap with treatment response biomarkers

Challenges

Bewildering number of potential COUs, just for treatment response

Overlap of treatment response with other types of COU

Treatment response may be more difficult to achieve because of biomarker variability both at baseline and at end-of-treatment

Research often in silos:
- MRI
- Ultrasound
- Pathology
- Artificial intelligence

Practical matters:
- Little coordination with Quantitative Imaging Biomarker Alliance (QIBA)
- Industry data often confidential and sensitive, so difficult to share
- Clinical validation studies are expensive and need industry and NIH support

Future Directions

To address these challenges:

- Feedback: To help this become a living document/talk, please let me know offline about any errors or omissions – in particular for any studies that are more convincing than the ones I discussed
- Need for a thorough or systematic literature review of NASH drug treatment response
- Organize treatment response biomarker efforts, if possible, through FDA BQP
- Encourage liaison with QIBA and Liver Forum Placebo groups
- Encourage sharing industry data to extent possible to further progress in treatment response
- Propose ***working group for treatment response***, within Liver Forum or elsewhere, to include interested stakeholders in pathology, ultrasound biomarkers, circulating biomarkers, and artificial intelligence, as well as MRI biomarkers

Thank you

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