Multicenter validation of association between decline in MRI-PDFF and histologic response in nonalcoholic steatohepatitis

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Abstract

Background: Emerging data from a single center study suggests that a 30% relative reduction in liver fat content as assessed by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) from baseline may be associated with histologic improvement in nonalcoholic steatohepatitis (NASH). There are limited multicenter data comparing an active drug versus placebo on the association between the quantity of liver fat reduction assessed by MRI-PDFF and histologic response in NASH.

Aim: To examine the association between 30% relative reduction in MRI-PDFF and histologic response in obeticholic acid versus placebo-treated patients in the FLINT trial.

Methods: This is a secondary analysis of the FLINT trial including 78 patients with MRI-PDFF measured before and after treatment along with paired liver histology assessment. Histologic response was defined as a two-point improvement in NAFLD Activity Score without worsening of fibrosis.

Results: Obeticholic acid at 25 mg orally once daily was better than placebo in improving MRI-PDFF by an absolute difference of −3.4% (95% CI, −6.5 to −0.2%, p-value=0.04), and relative difference of −17% (95% CI, −34 to 0%, p-value=0.05). The optimal cut-point for relative decline in MRI-PDFF for histologic response was 30%. (using Youden's index). The rate of histologic response in those who achieved < 30% decline in MRI-PDFF versus those who achieved a 30% decline in MRI-PDFF (*MRI-PDFF responders*) relative to baseline was 19% versus 50%, respectively. Compared to MRI-PDFF non-responders, MRI-PDFF responders demonstrated both a statistically and clinically significant higher odds 4.86 (95% CI, 1.4–12.8, p-value <0.009) of histologic response including significant improvements in both steatosis and ballooning.

Conclusions: Obeticholic acid was better than placebo in reducing liver fat. This multicenter trial provides novel data regarding the association between 30% decline in MRI-PDFF relative to baseline and histologic response in NASH.

Keywords

INTRODUCTION

Nonalcoholic steatohepatitis (NASH) is a chronic and progressive form of liver disease that can lead to cirrhosis, hepatocellular carcinoma and increased risk of both liver as well as all-cause mortality[1, 2]. It is commonly associated with obesity, metabolic syndrome and diabetes[3–5]. Although several therapies have shown promise in early phase trials there are currently no approved therapies for the treatment of NASH[6–8].

Liver histologic assessment is used for the assessment of treatment response in NASH[9]. Liver biopsy is an invasive procedure and may be associated with pain, infection, and risk of bleeding requiring blood transfusion; in extremely rare instances, it may cause death[10]. There is a major unmet need in the field to develop non-invasive biomarkers to assess histologic response in NASH without requiring a liver biopsy examination[11–13]. This need is driving intense research efforts to develop non-invasive modalities for this purpose.

The most commonly used metric for assessing treatment response in NASH trials is the NAFLD Activity Score (NAS). A summary score (range 0–8) based on steatosis (range 0–3), lobular inflammation (0–3) and ballooning (0–2), the NAS was developed to assess treatment response in the setting of a NASH trial[9]. Recent studies have shown that magnetic resonance imaging (MRI) derived biomarker termed proton-density-fat-fraction (PDFF) provides an accurate, non-invasive, reproducible, quantitative, and precise estimation of liver fat content[14–16].

Early phase single-center NASH trials have utilized MRI-PDFF as a primary outcome to assess treatment response [16–19]. Preliminary data from these trials have suggested an association between a 30% decline in MRI-PDFF from baseline and a two-point NAS improvement [20]. However, there are limited data from multicenter trials to validate this association[21]. To fill this gap in knowledge, we assessed the association between decline in MRI-PDFF and improvement in NAS in the Farnesoid X Receptor Ligand Obeticholic Acid in NASH (FLINT) trial[13] where we had obtained contemporaneous MRI-PDFF and liver biopsy before and after treatment in patients randomized to either obeticholic acid or placebo.

METHODS

Participants and study design:

This is a secondary analysis of the FLINT trial: a multicenter, randomized, double-masked, placebo-controlled, phase 2b clinical trial in which non-cirrhotic patients with biopsy-proven NASH were randomized to either obeticholic acid 25 mg orally daily or placebo for 72 weeks[13]. The FLINT trial included 283 patients who were recruited at eight sites of the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN), a consortium funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). All participants provided written informed consent and the studies were approved by the institutional review boards of the participating centers.

Inclusion and exclusion criteria:

> Detailed inclusion and exclusion criteria for the trial are published elsewhere[13]. Briefly, patients with biopsy-proven NASH and a NAS of at least 4 or higher were stratified by presence of diabetes and then randomized to either obeticholic acid or placebo. Patients with cirrhosis were excluded from the trial.

MRI assessment:

> Liver fat quantification was performed as a FLINT substudy using MRI-PDFF because of its demonstrated feasibility, accuracy, and precision in estimating liver fat longitudinally in the setting of a clinical trial [16, 17, 22]. MRI-PDFF was offered before and after treatment but was not a mandatory study procedure.

> The MRI protocol for the FLINT trial has been published elsewhere[14]. Liver MRI was obtained in 7 out of the 8 sites. Briefly, the inclusion criteria for the MRI-PDFF assessment were that the subject was enrolled in the FLINT trial, and that the subject was willing and able to complete two MRI exams (a baseline exam prior to randomization and an end of treatment MRI exam [both within 90 days of liver biopsy exam]). Exclusion criteria for the MRI sub-study were contraindications to MRI, extreme claustrophobia, pregnancy, weight or girth exceeding MRI scanner capability, or inability to complete the required study procedures in the opinion of the study investigators)[14].

> The NASH CRN Radiology Reading Center (RRC) in close collaboration with the NASH CRN Data Coordinating Center (DCC) managed the MRI portion of the FLINT trial[14]. All sites underwent a MRI sub-study qualification process and were certified by the RRC prior to initiating MRI exams on patients enrolled in the FLINT trial[14]. This rigor was felt to be important as this was one of the first multicenter clinical trials using MRI-PDFF in a NASH trial.

> MRI-PDFF analysis was performed at the RRC based at UCSD by experienced central readers under the supervision of experienced radiology investigators. The readers placed regions of interest in each of the nine Couinaud segments co-localized before and after treatment. The average PDFF across the nine segments was recorded at each time point. The readers and radiology investigators were masked to liver biopsy and clinical data as well as treatment group assignment.

Histologic assessment:

> The NASH CRN Histologic scoring system was used to assess liver histology before and after treatment by an experienced central pathology committee assessment[9]. The pathologists were masked to the sequence of liver biopsies as well as to clinical and imaging data and treatment group assignment.

Definition of Histologic response:

> Primary outcome of the FLINT trial was a 2-point improvement in NAS (a summary score [range 0–8] including steatosis [ranging 0–3], lobular inflammation [0–3], and ballooning

[0–2]) without worsening of fibrosis[9, 13]. This secondary analysis used the protocol defined definition to assess histologic response.

Statistical data analysis plan:

This analysis of the FLINT trial including 78 patients who underwent MRI-PDFF before and after treatment along with paired liver histology assessment. Association between quantitative change in MRI-PDFF and histologic response was assessed using robust linear and logistic regression models and their 95% confidence limits. Primary outcome was the primary endpoint of the FLINT Trial Histologic response, which was defined as a two-point improvement in NAFLD Activity Score without any worsening of fibrosis.

MRI-PDFF was not available at all sites. Therefore, a subset of patients underwent paired assessment. However, there was complete allocation concealment to the treatment group assignment, and the radiologists were masked to all clinical and histologic data.

RESULTS:

Baseline characteristics:

Seventy-eight patients (40 patients randomized to receive obeticholic acid and 38 patients randomized to placebo) with paired pre-treatment and post-treatment liver histology and MRI-PDFF data were included in this analysis. The baseline characteristics of the sub-study population are shown in Table 1. The two treatment groups were well matched for most clinical, biochemical and histologic features. The mean ±SD of the MRI-PDFF at was 18% ±9% in the obeticholic acid group and 20% ±10% in the placebo group

Decline in MRI-PDFF in obeticholic acid versus placebo:

Obeticholic acid, 25 mg orally once daily, was better than placebo in improving hepatic liver fat as assessed by MRI-PDFF with an absolute difference of −3.4% (95% CI, −6.5 to −0.2%, p-value=0.04), and relative difference of −17% (95% CI, −34 to 0%, p-value=0.05).

Association between MRI-PDFF decline and liver histology change:

An absolute decrease in MRI-PDFF of 4.8% (p-value<0.001) or a relative decrease in MRI-PDFF of 26% (p-value<0.001) from baseline was associated with a 1-point improvement in steatosis grade (Table 2). Data were consistent for both OCA and placebo groups.

Association between MRI-PDFF and weight change:

We also examined the association between changes in MRI-PDFF and weight change (Table 2). There was a clinically as well as statistically significant association between MRI-PDFF and weight change. We compared those who had 5% weight loss versus less than 5% weight loss and found that a 5% weight loss was associated with a 29% (95% CI, −51% to −8%, p-value <0.007) relative reduction in MRI-PDFF (Table 2).

Association between a 30% reduction in MRI-PDFF and histologic response:

Primary outcome: Greater reduction in MRI-PDFF was associated with greater odds of improvement in NAFLD activity score. We examined the optimal cut-point for relative

decline in MRI-PDFF using Youden's index and it was found to be 29.8 % (defined as MRI-PDFF responder). Then we divided the entire trial cohort (including OCA and placebo-treated patients) into those who had a 30% decline in MRI-PDFF (MRI-PDFF responders) versus < 30% decline in MRI-PDFF (MRI-PDFF non-responders). When comparing those with 30% reduction in MRI-PDFF versus those with < 30% reduction in MRI-PDFF, the proportion with a 2-point improvement in NAS without worsening of fibrosis was 50% versus 19% respectively, with statistically significant odds of histologic response (OR 4.86, 95% CI, 1.4–12.8, p-value <0.009, please see table 3.

Secondary outcomes (Table 3): When comparing MRI-PDFF responders versus MRI-PDFF non-responders, the rate of resolution of NASH was 20% versus 10%, and the proportion with a 1-stage improvement in fibrosis stage was 20% versus 19%, respectively and these trends were not statistically significant. The odds of resolution of NASH was 2.2 (95% CI, 0.5–8.6, p-value <0.27) and the odds of improvement in one-stage of fibrosis was OR 1.1 (95% CI, 0.3–3.8, p-value 0.92), respectively.

When comparing MRI-PDFF responders versus MRI-PDFF non-responders,, the proportion with a 1-point improvement in steatosis grade was 85% versus 25% as expected with an odds ratio of 14.9 (95% CI, 3.8–57.7, p-value <0.001), respectively; and the rate of 1-point improvement in ballooning was 50% versus 26% with an odds ratio of 2.9 (95% CL, 1.0–8.2, p-value <0.05). There was no significant association between change in MRI-PDFF and lobular inflammation and portal inflammation.

In sensitivity analysis, we examined the optimal cut-point of MRI-PDFF that was associated with histologic response. The optimal cut-point of MRI-PDFF associated with histologic response in this trial was 29.8% relative MRI-PDFF reduction, which was statistically significant (P-value < 0.05) as shown in Table 4. In addition, as shown in figure 2, greater reduction in MRI-PDFF was associated even higher odds of histologic response.

Sub-group analysis by weight loss and ALT response (supplementary Table 1a and 1b):

We also analyzed the data stratified by weight loss of 5% versus < 5%, and ALT decline by 17 IU/L versus < 17 IU/L for histologic response. These data are shown in supplementary Table 1a and 1b. The rate of histologic response among those who achieved 5% weight loss versus < 5% was 43% and 23, p-value 0.14. The rate of histologic response among those who had a relative decline in ALT by 17 IU/L versus < 17 IU/L was 37% and 19%, respectively, p-value 0.07. Among the three response variables including MRI-PDFF 30% decline versus weight loss 5% versus ALT decline 17 IU/L, only MRI-PDFF responders showed a significant association with histologic response.

DISCUSSION:

Main findings:

This secondary analysis of the FLINT trial provides novel paired MRI-PDFF and liver histology data over 72 weeks in the setting of a multicenter clinical trial. Obeticholic acid was better than placebo in reducing liver fat as assessed by MRI-PDFF. This multicenter trial provides validation data regarding the association between histologic response and a

30% decline in MRI-PDFF relative to baseline. This study provides novel data on the clinically relevant decline in liver fat that may be associated with histologic response in NASH in a NASH trial. This helps validate that a 30% decline in MRI-PDFF may be used as a potential treatment response criteria for early phase clinical trials in NASH when a reduction in liver fat is targeted.

In context with published literature:

Patel and colleagues have previously shown that a 30% decline in MRI-PDFF is associated with 2-point improvement in NAFLD activity score[20]. These data were recently confirmed in a Phase 2b trial of selonsertib treatment with or without simtuzumab over a 24-week period showing that a 30% decline in liver fat was associated with higher odds of histologic response [23]. In the ASK-1 trial of selonsertib, a 30% decline in liver fat was statistically significantly associated with higher odds in reduction in steatosis grade as well as a 2-point improvement in NAS[23]. In the current study, we provide a validation of the concept that at a threshold of 30% reduction in liver fat is associated with histologic improvements by 2 points in NAFLD Activity Score without worsening of fibrosis. Whether this finding applies to improvements seen with other therapies will need to be established. Furthermore, we also found trends in higher odds of improvement in ballooning and resolution of NASH. There was no significant improvement seen in fibrosis. In addition, a 5% weight loss is associated with a significant decline in liver fat by MRI-PDFF as previously shown[24].Allen and colleagues have recently suggested the role of 3D MRE in assessing changes after bariatric surgery and these may be helpful in assessing treatment response in future studies in addition to MRI-PDFF[25]. Furthermore, Harrison and colleagues have recently demonstrated that Resmetirom, a thyroid β receptor agonist, is associated with significant reduction in MRI-PDFF and it may be associated with improvement in liver histology in patients with biopsy-proven NASH.[26]

Strengths and limitations:

Strengths of this study include the use of multicenter trial including 78 patients who underwent paired MRI-PDFF and liver biopsy assessment over a 72 week period. This is longest trial with paired MRI-PDFF and liver biopsy assessment to date. The MRI-PDFF was centrally read and both radiologists and pathologists were masked to clinical as well as pathology and radiology data, respectively. The baseline MRI-PDFF between the OCA and the placebo group was similar. We acknowledge following limitations. MRI-PDFF was only available in a subset of FLINT trial participants. This trial did not include magnetic resonance elastography (MRE) or vibration controlled transient elastography assessment so we were not able to assess changes in elastography in this trial and its association with changes in liver histology or MRI-PDFF[27–29]. Therefore, future studies are needed to incorporate a more detailed elastography based assessment in the setting of NASH trials. Furthermore, this study was of a modest size and thus lacked the power to detect differences in changes in liver fat and fibrosis progression or regression[30]. Therefore, future studies with larger sample sizes are needed to better understand the temporal association between changes in MRI-PDFF and fibrosis change in the setting of NASH trials[30, 31].

Implications for future research and clinical trial design:

MRI-PDFF is an accurate measure of liver fat content and has the advantage compared to histology in providing a continuous variable is assessing quantitative changes in liver fat in the setting of treatment trials[12, 15, 30, 32, 33]. However, it is neither designed nor capable of providing an estimate in the changes in other key variables associated with changes in disease activity and severity in NASH and NASH-related fibrosis, respectively[34]. In this study, we demonstrated that when there is a significant reduction in MRI-PDFF beyond a threshold of 30% then improvements in other features related to disease activity such as ballooning, lobular inflammation, or steatosis are also more likely to be seen. These data suggest that a relative reduction of MRI-PDFF of at least 30% is a useful clinical biomarker for early phase clinical trials given its association with a 2-point improvement in NAS along with improvements in steatosis and ballooning. Quantitative biomarkers of liver inflammation, ballooning, Mallory-Denk bodies and fibrosis are still needed in combination with MRI-PDFF in future trials for assessment of treatment response[35, 36].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Appendix:

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Abbreviations:

NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
MRI	magnetic resonance imaging
PDFF	proton-density-fat-fraction
NAS	NAFLD Activity Score
ROI	region of interest
BMI	body mass index
ROC	receiver operating characteristic
AUROC	area under receiver operating characteristic

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Histologic improvement in NASH by relative 72-week change in MRI-PDFF
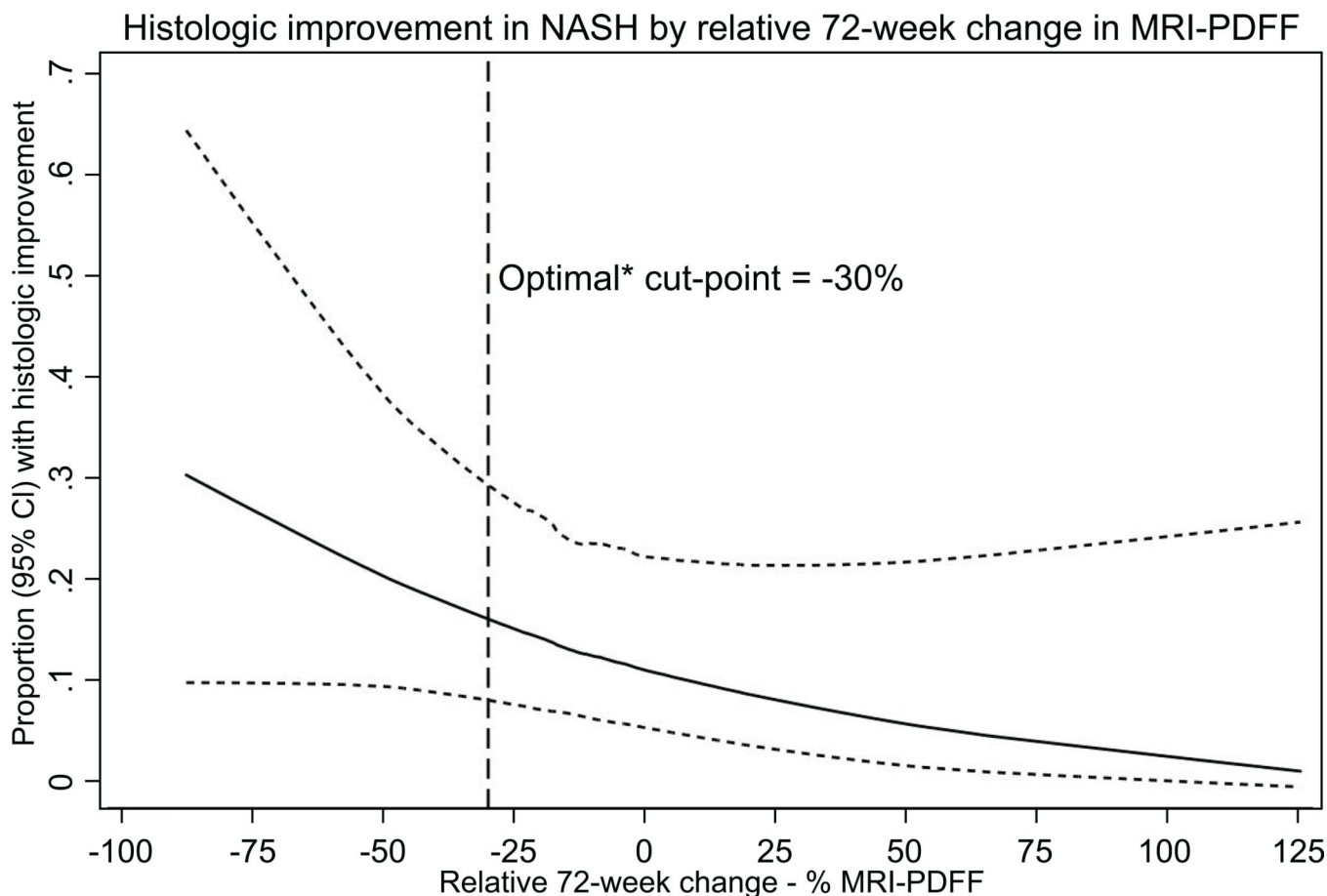
*Based on Youden's index

Figure 1: Histologic response in NASH increases as relative decline in MRI-PDFF increases
The y axis represents the proportion of patients who achieved histologic response and the X-axis denotes relative change (decrease towards the left and increase towards the right) in MRI-PDFF. These data include both the OCA and the placebo group. The dotted vertical line represents the optimal cut-point for MRI-PDFF decline at 30% (p-value < 0.05%)

Table 1.

Baseline characteristics by treatment group

	Obeticholic Acid (n=40)	Placebo (n=38)	P-value
Demographics			
Age – yr	53 (9)	52 (13)	0.71
Male sex – no. (%)	15 (38%)	14 (37%)	0.95
White race – no. (%)	35 (88%)	32 (84%)	0.68
Hispanic ethnicity – no. (%)	7 (18%)	6 (16%)	0.84
Liver enzymes			
Alanine aminotransferase – U/L	80 (41)	68 (33)	0.14
Aspartate aminotransferase – U/L	57 (32)	50 (25)	0.30
Alkaline phosphatase – U/L	76 (25)	76 (24)	0.96
γ-Glutamyltransferase – U/L	80 (103)	61 (46)	0.28
Total bilirubin – mg/dL	0.7 (0.3)	0.6 (0.3)	0.35
Lipids			
Cholesterol			
Total – mg/dL	192 (42)	194 (48)	0.87
High-density lipoprotein – mg/dL	44 (13)	44 (15)	0.83
Low-density lipoprotein – mg/dL	110 (36)	115 (40)	0.57
Trigylcerides – mg/dL	193 (89)	180 (17)	0.57
Metabolic factors			
Fasting serum glucose – mg/dL	117 (35)	107 (28)	0.16
Insulin – umol/mL	39 (56)	21 (15)	0.06
HOMA–IR$^{\|}$ – mg/dL × umol/mL / 405	12.4 (18.6)	3.8 (6.0)	0.04
Hemoglobin A1c – %	6.4 (1.1)	6.3 (0.9)	0.56
Weight – kg	97 (18)	94 (15)	0.41
Body–mass index – kg/m^2	34 (5)	33 (5)	0.19
Waist circumference – cm	113 (12)	108 (11)	0.07
Waist to hip ratio	0.97 (0.07)	0.94 (0.07)	0.04
Systolic blood pressure – mmHg	132 (15)	133 (16)	0.80
Diastolic blood pressure – mmHg	78 (10)	79 (11)	0.33
Comorbidities			
Hyperlipidemia¶ – no. (%)	21 (52%)	20 (53%)	0.99
Hypertension – no. (%)	20 (50%)	21 (55%)	0.64
Cardiovascular disease – no. (%)	0 (0%)	1 (3%)	0.30
Diabetes – no. (%)	20 (50%)	20 (53%)	0.82
Concomitant medications in the past 6 months			

	Obeticholic Acid (n=40)	Placebo (n=38)	P-value
Antilipidemic – no. (%)	19 (48%)	15 (39%)	0.48
Cardiovascular/hypertensive – no. (%)	24 (60%)	27 (71%)	0.30
Antidiabetic – no. (%)	22 (55%)	21 (55%)	0.98
Metformin – no. (%)	20 (50%)	19 (50%)	1.00
Pioglitazone – no. (%)	0 (0%)	1 (3%)	0.30
Vitamin E – no. (%)	7 (18%)	12 (32%)	0.15
Aspirin – no. (%)	10 (25%)	12 (32%)	0.52
Liver histology findings			
Definite steatohepatitis – no. (%)	31 (78%)	30 (79%)	0.88
Fibrosis – stage [†]	1.9 (1.1)	1.7 (1.1)	0.59
Total NAFLD activity score[‡]	5.1 (1.3)	5.4 (1.4)	0.29
Hepatocellular ballooning – score	1.4 (0.8)	1.4 (0.7)	0.91
Steatosis – score	1.9 (0.8)	2.1 (0.8)	0.32
Lobular inflammation – score	1.8 (0.7)	1.9 (0.8)	0.47
Portal inflammation – score[§]	1.2 (0.6)	1.2 (0.6)	0.76
MRI-PDFF - %			
Mean (SD)	18 (9)	20 (10)	0.41
Median [IQR]	19 [10, 23]	17 [12, 25]	

[*] Plus–minus values are means±SD.

[¶] High cholesterol or high triglyerides

[†] Fibrosis was assessed on a scale of 0 to 4, with higher scores indicating more severe fibrosis.

[‡] Total nonalcoholic fatty liver disease (NAFLD) activity was assessed on a scale of 0 to 8, with higher scores indicating more severe disease; the components of this measure are steatosis (assessed on a scale of 0 to 3), lobular inflammation (assessed on a scale of 0 to 3), and hepatocellular ballooning (assessed on a scale of 0 to 2).

[§] Portal inflammation was assessed on a scale of 0 to 2 with higher scores indicating more severe inflammation.

[∥] Homeostasis Model Assessment-estimated Insulin Resistance

Table 2.

Association of 72-week change in MRI-PDFF with treatment and changes in steatosis score and weight

Independent variable	Change in MRI-PDFF	Difference / slope*	95% CI	P-value
OCA vs placebo	Absolute	−3.4%	−6.5, −0.2	0.04
	Relative	−17%	−34, 0	0.05
Change in steatosis	Absolute	4.9% / score	3.2, 6.6	<0.001
	Relative	26% / score	18, 35	<0.001
Change in weight	Absolute	0.7% / kg	0.4, 1.0	<0.001
	Relative	2.8% / kg	1.3, 4.3	<0.001
Weight loss 5% vs <5% †	Absolute	−7.9%	−11.7, −4.1	<0.001
	Relative	−29%	−51, −8	0.007

*Estimated using robust regression adjusting for baseline MRI-PDFF

†18% (14/78) patients lost 5% body weight

Table 3.

Performance diagnostics of 72-week relative change in PDFF in assessing histologic improvement and resolution of NASH

Event	Prevalence of event	Cross-validated AUROC (95% CI)	Cutoff criteria	Cutoff (Relative change in PDFF)	Sens	Spec	PPV	NPV
Histologic improvement	27%	0.60 (0.45, 0.75)	Sens = 90%	23.1%	Fixed	23%	30%	87%
			Spec = 90%	−57.3%	10%	Fixed	29%	73%
			Youden's index	−29.8%	48%	81%	48%	81%

Table 4.

Association of at least 30% relative decrease at 72 weeks in MRI-PDFF with histologic outcomes

	Relative Decrease in MRI-PDFF		30% vs <30% Relative Decrease in MRI-PDFF		
Histologic Outcome (1+ score/stage decrease)	**30% (n=20)**	**<30% (n=58)**	**Odds Ratio**	**95% CI**	**P-value**
Steatosis	85%	28%	14.9	3.8, 57.7	**<0.001**
Lobular Inflammation	45%	45%	1.0	0.4, 2.8	0.99
Portal inflammation	15%	12%	1.3	0.3, 5.5	0.74
Ballooning	50%	26%	2.9	1.0, 8.2	**0.05**
Fibrosis	20%	19%	1.1	0.3, 3.8	0.92
Histologic improvement [*]	50%	19%	4.3	1.4, 12.8	**0.009**
Resolution of NASH	20%	10%	2.2	0.5, 8.6	0.27

[*] Decrease in NAFLD Activity Score (NAS) of at least 2 points and no worsening of fibrosis