Treatment with Resmetirom Improves Symptom Burden in Patients with Metabolic Dysfunction-Associated Steatohepatitis (MASH)

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BACKGROUND

- Metabolic dysfunction-associated steatohepatitis (MASH) is characterized by substantial health-related quality of life (HRQL) impairment and symptom burden.
- Patients with MASH frequently experience fatigue, abdominal symptoms, cognitive impairment, and disease-related distress that can affect daily functioning and well-being.
- These patient-reported aspects of disease are not captured by histologic or biomarker-based measures, supporting the use of disease-specific patient-reported outcome instruments to assess treatment benefit.

AIM

- The aim was to evaluate the effect of treatment with resmetirom on MASH-specific symptoms using the CLDQ-MASH Symptom Questionnaire (CLDQ-MASH-SQ).

METHODS

- This post-hoc analysis included patients with MASH enrolled in the phase 3 MAESTRO-NAFLD-1 and MAESTRO-NASH studies.
- Patients were stratified as early MASH (VCTE 5.5 to <8.5 kPa), or MASH with histologic F2-F3 fibrosis, or MASH with well-compensated cirrhosis.
- Patients with early MASH and MASH F2-F3 received resmetirom 80 mg, resmetirom 100 mg, or placebo for 52 weeks; patients with MASH cirrhosis received resmetirom 80 mg.
- Symptoms were assessed using the CLDQ-MASH-SQ (36 items, 8 domains scored 1-7, higher scores indicate better HRQL, lower symptom burden); changes from baseline to week 52 were evaluated.

RESULTS

- A total of 2066 MASH patients were included (n=1037 early MASH, n=869 F2-F3, n=160 cirrhosis).
- The baseline symptom burden increased with disease severity in all domains (p<0.01) (**Figure 1**).
- The greatest worsening with increasing disease severity was in symptoms related to disease-related distress, fatigue and physical weakness, various peripheral symptoms (itching, dry mouth, muscle cramps), and pain or physical discomfort.

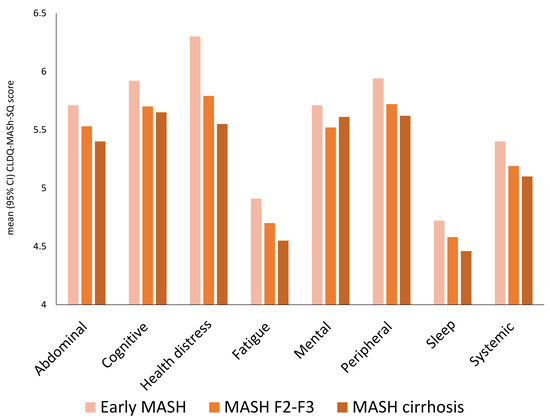


Figure 1. Baseline CLDQ-MASH-SQ domain scores by liver disease severity

RESULTS

- At week 52, patients with early MASH treated with either 100 mg or 80 mg of resmetirom showed significant improvements (mean change from baseline (95% CI)) in the domains of:
  - **Abdominal symptoms**: +0.14 (0.02, 0.25) and +0.18 (0.04, 0.31), respectively;
  - **Health distress**: +0.19 (0.08, 0.29) and +0.18 (0.08, 0.28), respectively;
  - No significant improvement in these domains was observed with placebo (p>0.05).
- Among MRI-PDFF responders (≥30% reduction regardless of treatment), the mean (95% CI) improvements were +0.16 (0.06, 0.26) for Abdominal symptoms and +0.17 (0.08, 0.25) for Health distress (**Figure 2**).
- At the item level, in addition to improvements in symptom items of the Abdominal symptoms and Health distress domains, MRI-PDFF responders had improvements in anxiety and feeling unhappy symptoms (**Table 1**).

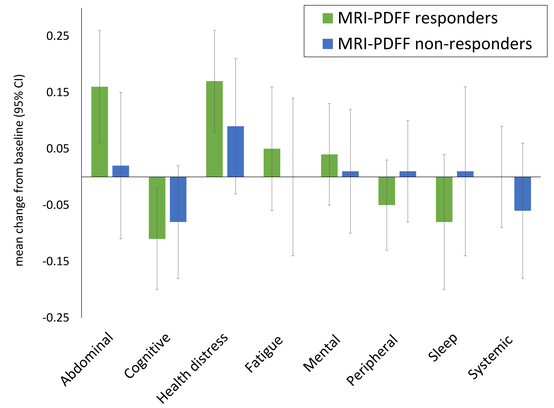


Figure 2. Changes in CLDQ-MASH-SQ scores of patients with early MASH by the presence of MRI-PDFF response

Table 1. Changes in CLDQ-MASH-SQ item scores of patients with early MASH by the presence of MRI-PDFF response

CLDQ-MASH-SQ item	MRI-PDFF responders	P_0 in responders	MRI-PDFF non-responders	P_0 in non-responders	P responder to non-responder
Being frustrated about liver disease	0.14 (0.03, 0.25)	0.0147	0.08 (-0.06, 0.22)	0.19	0.49
Feeling weighed down by liver problems	0.09 (-0.02, 0.19)	0.0620	0.06 (-0.06, 0.18)	0.29	0.58
Feeling of abdominal bloating	0.35 (0.20, 0.51)	<.0001	0.16 (-0.03, 0.35)	0.0636	0.33
Being tired or fatigued	0.17 (0.03, 0.32)	0.0310	0.15 (-0.03, 0.34)	0.16	0.97
Abdominal pain	0.18 (0.05, 0.31)	0.0055	0.02 (-0.15, 0.19)	0.88	0.28
Feeling anxious	0.17 (0.03, 0.30)	0.0106	-0.05 (-0.21, 0.11)	0.50	0.0452
Feeling unhappy	0.14 (0.01, 0.26)	0.0412	-0.06 (-0.21, 0.10)	0.45	0.0364
Abdominal discomfort	0.18 (0.05, 0.31)	0.0178	0.04 (-0.12, 0.21)	0.56	0.54
Feeling distressed by having MASH	0.29 (0.18, 0.39)	<.0001	0.12 (-0.03, 0.27)	0.0631	0.0906

MRI-PDFF response was defined as at least 30% decrease from baseline, regardless of treatment regimen
The domain and item score changes from baseline to week 52 are presented as mean (95% CI), with p-values P_0 returned by tests for difference from zero (no significant change).

RESULTS

- In patients with MASH F2-F3, Health distress domain scores improved significantly from baseline across treatment groups (**Figure 3**, **Table 2**).

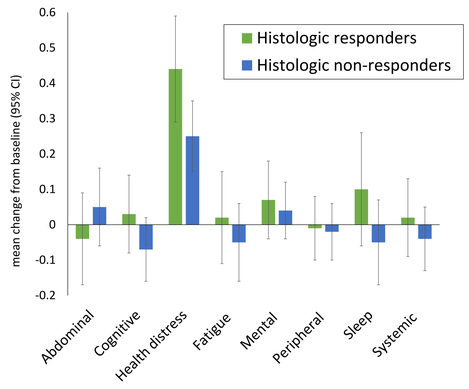


Figure 3. Changes in CLDQ-MASH-SQ scores of patients with MASH F2-F3 by the presence of histologic response

Table 2. Changes in CLDQ-MASH-SQ scores of patients with MASH F2-F3 by the presence of histologic response.

CLDQ-MASH-SQ symptom item	Histologic responders	P_0 in responders	Histologic non-responders	P_0 in non-responders	P responder to non-responder
Being frustrated about liver disease	0.42 (0.23, 0.62)	<.0001	0.20 (0.06, 0.34)	0.0021	0.0244
Feeling weighed down by liver problems	0.41 (0.23, 0.58)	<.0001	0.20 (0.08, 0.33)	0.0025	0.0341
Feeling a decreased level of energy	0.16 (-0.02, 0.33)	0.0839	-0.09 (-0.24, 0.05)	0.23	0.0331
Feeling unhappy	0.15 (-0.02, 0.31)	0.0950	0.04 (-0.09, 0.17)	0.61	0.66
Dry mouth	0.20 (0.02, 0.39)	0.0444	-0.14 (-0.29, 0.01)	0.0475	0.0151
Feeling distressed by having MASH	0.49 (0.34, 0.65)	<.0001	0.33 (0.19, 0.46)	<.0001	0.10

Histologic response was defined as resolution of MASH without worsening of fibrosis or improvement of fibrosis without worsening of MASH, regardless of treatment regimen; The domain and item score changes from baseline to week 52 are shown as mean (95% CI), p-values P_0 returned by tests for difference from zero (no significant change).

- Among patients with well-compensated MASH cirrhosis treated with resmetirom 80 mg, Health distress domain score improved by +0.21 (95% CI 0.00 to 0.43; p=0.052) at week 52; improvement in frustration about liver disease item was +0.28 (0.02 to 0.55; p=0.047).
- Among VCTE responders with cirrhosis (≥25% reduction in LSM), the bleeding gums score improved by +0.40 (0.01 to 0.79) vs -0.11 (-0.36 to 0.15) in non-responders (p=0.031); the joint pain score improved by +0.27 (-0.09 to 0.63) vs -0.22 (-0.54 to 0.11) (p=0.048).

CONCLUSIONS

- **Across the spectrum of MASH, treatment with resmetirom and response to treatment were associated with improvements in multiple aspects of disease-specific symptom burden.**
- **Patient-reported symptom assessment may capture aspects of therapeutic benefit beyond traditional efficacy endpoints.**

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