Use of non-invasive tests to diagnose and follow MASH with liver fibrosis patients treated with resmetirom

Naim Alkhouri[1], Sam Moussa[2], Arun J. Sanyal[3], Rebecca Taub[4], Dominic Labriola[4], Mazen Noureddin[5]

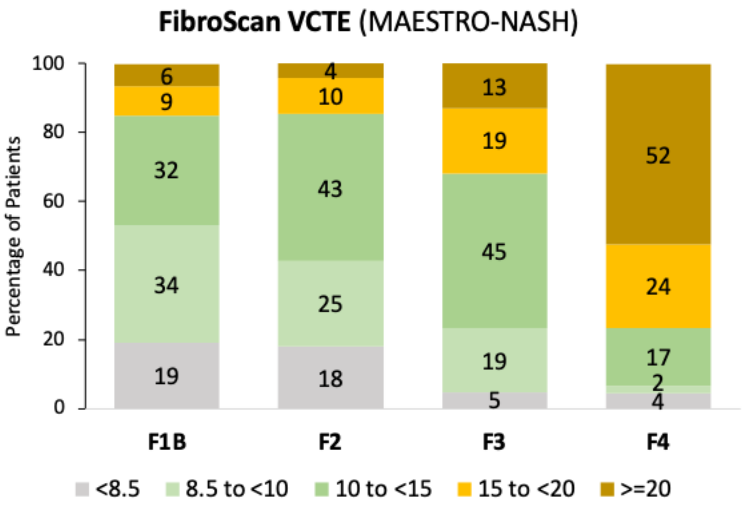
1: Arizona Liver Health, Phoenix, AZ, USA; 2: University of Arizona, Tuscon, AZ, USA; 3: Virginia Commonwealth University Richmond, VA, USA; 4: Madrigal Pharmaceuticals, West Conshohocken, PA, USA; 5: Houston Methodist Hospital, Houston, TX, USA

Background: MAESTRO-NASH (NCT03900429) is an ongoing 54-month, randomized, double-blind, placebo-controlled phase 3 trial evaluation the efficacy of resmetirom in patients with biopsy-confirmed metabolic dysfunction-associated steatohepatitis (MASH) and fibrosis. 966 patients with biopsy-confirmed MASH were randomized 1:1:1 to resmetirom 80 mg, resmetirom 100 mg, or placebo administered once daily. Dual primary endpoints at Week 52 were achieved with both resmetirom 80 mg and 100 mg: MASH resolution with no worsening of fibrosis (NR) or ≥ 1-stage improvement in fibrosis with no worsening of NAS (FI). Both Week 52 liver biopsy endpoints, NR and FI, were achieved. Resmetirom was recently approved for the treatment of adult patients with noncirrhotic MASH and liver fibrosis consistent with F2 to F3 stages. Accuracy of MASH/fibrosis diagnosis and follow-up of resmetirom treated patients long-term using real-world, readily available non-invasive testing were assessed.

Material and Methods: Machine learning models evaluated the relative importance of MAESTRO patient's intrinsic characteristics and screening/baseline biomarkers in 1247 patients who had F0-F4 on liver biopsy. The Random Forest (RF) model was selected due to its predictive performance. For this model, only readily available tests including FibroScan, ELF and standard blood chemistries were used to determine the accuracy in diagnosing MASH patients consistent with F2 to F3. Long-term effects of resmetirom on non-invasive tests and biomarkers out to 3 years post randomization were evaluated.

Results: Using 23 baseline clinical characteristics, standards labs, FibroScan and ELF, the random forest model determined that the most important markers that distinguished F2 to F3 from either F0/1 or F4, in order were FibroScan VCTE, platelets, FIB-4, FAST and ELF. The AUC (SD) for separation from F0/1 or F4 were 0.76 (0.03) and 0.90 (0.03), respectively. 58% of F2 to F3 were correctly predicted to be F2/F3; 26% were incorrectly predicted to be F0/F1 and 16% were incorrectly predicted to be F4. Of F4 patients, 72% were correctly predicted to be F4 and 19% were predicted to be F2/F3. The addition of MRE/MRI-PDFF increased diagnostic accuracy for F2/F3 to 68% and F4 to 81%. The figure below illustrates how varying VCTE thresholds can aid in effectively identifying the F2/F3 population. Resmetirom showed improvement relative to placebo on multiple responses at Week 52 including MRI-PDFF (the most predictive of a biopsy response), liver enzymes, lipids, and FibroScan CAP and VCTE.

Conclusions: Reasonably accurate identification of MASH F2/F3 patients was achieved with FibroScan VCTE, ELF and readily available blood tests. F4 patients were effectively rule out.


FibroScan VCTE (MAESTRO-NASH)
Percentage of Patients
100
80
60
40
20
0
6
9
32
34
19
4
10
43
25
18
13
19
45
19
5
52
24
17
2
4
F1B
F2
F3
F4
<8.5
8.5 to <10
10 to <15
15 to <20
>=20