Correlation of non-invasive tests with histological features and intrahepatic Z-alpha-1 antitrypsin burden in patients with alpha-1 antitrypsin deficiency-associated liver disease

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Introduction

- Alpha-1 antitrypsin deficiency (AATD) is a genetic disease characterized by low levels of serum alpha-1 antitrypsin (AAT), a liver-derived serine protease inhibitor (Pi) that maintains the protease–antiprotease balance in the lungs.[1]
- The Pi*ZZ genotype produces misfolded AAT (Z-AAT), resulting in hepatic Z-AAT aggregates and reduced antiprotease activity in the lungs.[1]
- AATD-associated liver disease (AATD-LD), signified by fibrosis, may develop owing to increased cellular stress, apoptosis, inflammation and fibrogenesis.[2–4]
- Currently, no pharmacological treatments exist[2] and reliable non-invasive tests (NITs) are limited for AATD-LD.
  - Fazirsiran is an investigational small interfering RNA undergoing phase 3 development in patients with AATD-LD (NCT05677971).

Objective

- To leverage baseline data from two phase 2 clinical trials of fazirsiran to investigate the correlations of NITs with liver disease burden in patients with AATD-LD.

Methods

- Baseline serum and histology data were used from patients with AATD-LD treated with fazirsiran or placebo in the phase 2 AROAAT-2001 (NCT03945292)[5] and AROAAT-2002 (NCT03946449)[6] trials.
- Histological features comprised meta-analysis of histological data in viral hepatitis (METAVIR) fibrosis/cirrhosis stage, portal inflammation and periodic acid-Schiff staining with diastase (PAS-D) globule burden.
- NITs comprised alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), pro-peptide of type III collagen (Pro-C3), aspartate aminotransferase-to-platelet ratio index (APRI), fibrosis-4 (FIB-4), liver stiffness measurement (LSM) via FibroScan® and serum Z-AAT.
- Serum and total intrahepatic Z-AAT were analysed by liquid chromatography-mass spectrometry (LC-MS).[6]
- Baseline correlations of NITs with intrahepatic Z-AAT (total, soluble and insoluble) and liver histological features were evaluated by Spearman correlation analysis.
- Correlations of fibrosis- and fibrogenesis-related NITs (LSM via FibroScan®, Pro-C3 and serum Z-AAT) with METAVIR fibrosis/cirrhosis stage were evaluated by Kruskal–Wallis analysis.
- The performance of individual NITs on the identification of patients with AATD-LD and significant (F2–4) or advanced (F3–4) fibrosis/cirrhosis were evaluated by area under the receiver operating characteristic (AUROC) analysis.
- Further methodological details are described in Strnad P *et al. N Engl J Med* 2022.[6]

Table 1. Demographics and baseline characteristics of patients with recorded fibrosis

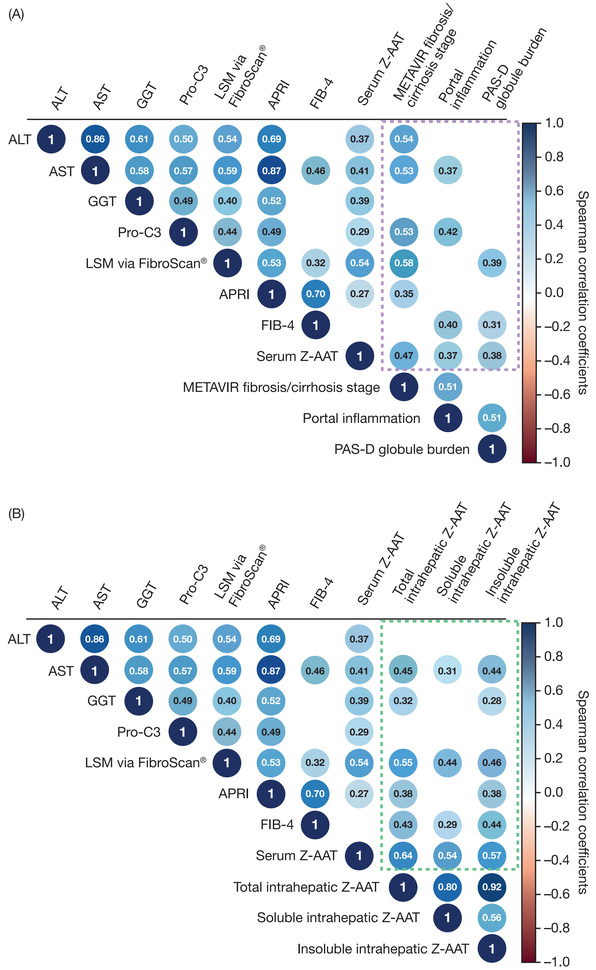
	Overall (N = 40)	AROAAT-2001 (n = 25)	AROAAT-2002 (n = 15)
Age, years, mean (SD)	54.2 (12.2)	55.0 (11.4)	52.9 (13.8)
Male, n (%)	27 (67.5)	14 (56.0)	13 (86.7)
Non-Hispanic or Latino, n (%)	37 (92.5)	22 (88.0)	15 (100)
BMI, kg/m^2, mean (SD)	28.4 (6.7)	30.4 (7.3)	25.1 (4.1)
NITs, mean (SD)			
AST (U/L)	36.7 (14.0)	32.7 (11.3)	43.3 (15.8)
ALT (U/L)	46.0 (24.5)	34.8 (15.3)	64.5 (25.9)
GGT (U/L)	69.8 (119.3)	42.8 (32.2)	114.9 (185.4)
Pro-C3 (ng/mL)	16.6 (5.1)	14.8 (3.4)	19.6 (6.1)
LSM via FibroScan® (kPa)	8.8 (4.3)	8.0 (4.1)	9.9 (4.6)
METAVIR fibrosis/cirrhosis stage, n (%)[a]			
F0	4 (10.0)	3 (12.0)	1 (6.7)
F1	11 (27.5)	9 (36.0)	2 (13.3)
F2	17 (42.5)	11 (44.0)	6 (40.0)
F3	6 (15.0)	2 (8.0)	4 (26.7)
F4	2 (5.0)	0	2 (13.3)

[a]Among patients who were identified as having liver fibrosis based on local pathology reading, baseline liver biopsies were re-read centrally and served as the baseline METAVIR fibrosis/cirrhosis stage.[6]

Results

- Of 56 patients from the AROAAT-2001 (n = 40) and AROAAT-2002 (n = 16) studies, 40 patients had a recorded METAVIR fibrosis/cirrhosis stage at baseline: F0, n = 4 (10.0%); F1, n = 11 (27.5%); F2, n = 17 (42.5%); F3, n = 6 (15.0%); and F4, n = 2 (5.0%) (**Table 1**).
- Many commonly available and emerging NITs demonstrated significant correlations ($p < 0.05$) with liver histological features in patients with AATD-LD (**Figure 1A**).
  - ALT, AST, Pro-C3, LSM via FibroScan®, APRI and serum Z-AAT correlated with METAVIR fibrosis/cirrhosis stage.

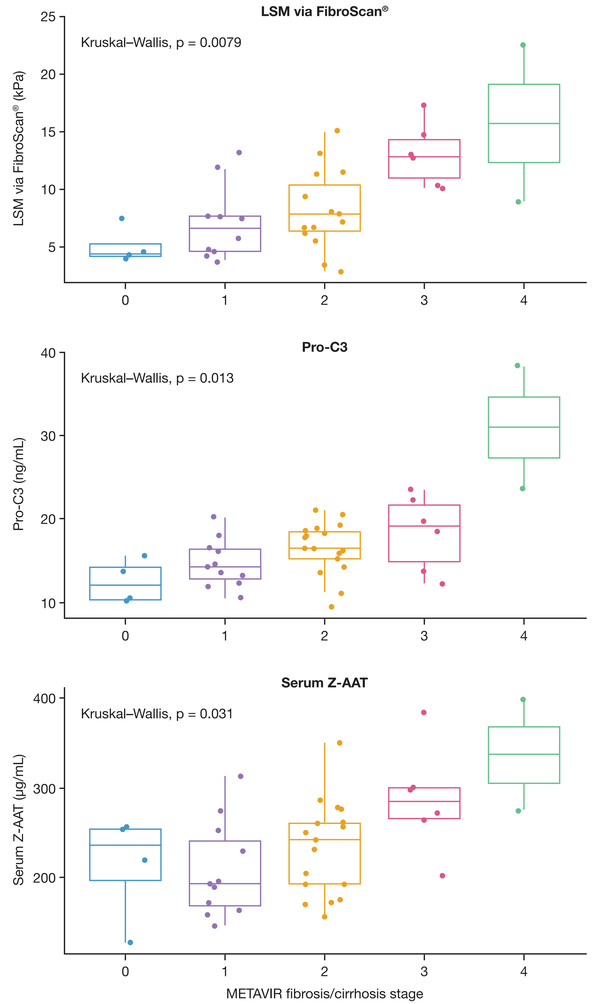
Figure 1. Correlations (A) between NITs and liver histological features and (B) between NITs and intrahepatic Z-AAT in patients with AATD-LD



Circles indicate significant correlations ($p < 0.05$).
Spearman correlation coefficients range from −1 to +1, where −1 means very strong negative correlation and +1 means very strong positive correlation.
Correlations between NITs and liver histological features are highlighted by the purple dashed box. Correlations between NITs and intrahepatic Z-AAT are highlighted with the green dashed box.

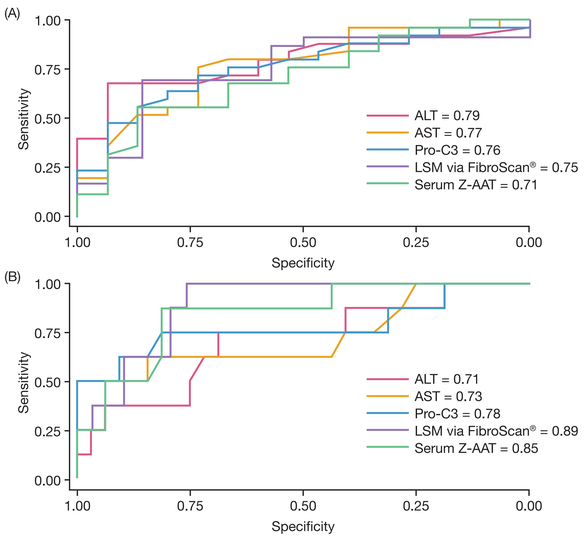
- AST, Pro-C3, FIB-4 and serum Z-AAT correlated with portal inflammation.
- LSM via FibroScan®, FIB-4 and serum Z-AAT correlated with PAS-D globule burden.
- Similarly, intrahepatic Z-AAT burden (measured by LC-MS) significantly correlated ($p < 0.05$) with several NITs (**Figure 1B**).
  - ALT, AST, Pro-C3, LSM via FibroScan®, APRI and serum Z-AAT significantly correlated with total intrahepatic Z-AAT.
- Fibrosis- and/or fibrogenesis-related NITs (LSM via FibroScan®) and serum Z-AAT significantly correlated with METAVIR fibrosis/cirrhosis stage (**Figure 2**).
- ALT, AST, LSM via FibroScan®, Pro-C3 and serum Z-AAT had AUROC scores of ≥ 0.70 for the identification of patients with F2–4 fibrosis/cirrhosis (**Figure 3A**) and with F3–4 fibrosis/cirrhosis (**Figure 3B**).

Figure 2. Fibrosis- and fibrogenesis-related NITs and serum Z-AAT by METAVIR fibrosis/cirrhosis stage



Kruskal–Wallis analysis was used to evaluate the correlations between fibrosis- and fibrogenesis-related NITs and METAVIR fibrosis/cirrhosis stage.

Figure 3. Performance characteristics of NITs for the identification of patients with AATD-LD and (A) significant (F2–4) fibrosis/cirrhosis and (B) advanced (F3–4) fibrosis/cirrhosis using AUROC analyses



Conclusions

- The study identified correlations of NITs (ALT, AST, Pro-C3, APRI, FIB-4, LSM via FibroScan® and serum Z-AAT) to liver histological features (METAVIR fibrosis/cirrhosis stage, portal inflammation and PAS-D globule burden), and intrahepatic Z-AAT burden (total, soluble and insoluble; analysed by LC-MS).
- ALT, AST, LSM via FibroScan®, Pro-C3 and serum Z-AAT demonstrated good discriminatory performance in the identification of patients with F2–4 and F3–4 fibrosis/cirrhosis.
  - The combination of these NITs and additional future novel NITs may improve performance for the identification of patients with AATD-LD and significant (F2–4) or advanced (F3–4) fibrosis/cirrhosis; therefore, further investigation is warranted.
- Findings from the current study were based on the limited numbers of patients with AATD-LD and is focused on cross-sectional correlations; clinical utility of these NITs in the identification of patients with AATD-LD with liver fibrosis and in monitoring treatment responses requires validation in larger and longitudinal studies

Abbreviations

AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency; ALT, alanine aminotransferase; APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristic; BMI, body mass index; FIB-4, fibrosis-4; GGT, gamma-glutamyl transferase; LC-MS, liquid chromatography-mass spectrometry; LSM, liver stiffness measurement; METAVIR, meta-analysis of histological data in viral hepatitis; NIT, non-invasive test; PAS-D, periodic acid-Schiff staining with diastase; Pi, protease inhibitor; Pro-C3, pro-peptide of type III collagen; SD, standard deviation; Z-AAT, misfolded alpha-1 antitrypsin.

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References

References can be found in the supplementary material accessed via the QR code.

Disclosures

J-CC, **RH**, **FH**, **MDP**, **JC**, **SG**, **NKD** and **PT** are employees and stockholders of Takeda Development Center Americas, Inc. **TS** is an employee of Arrowhead Pharmaceuticals. **RL** serves as a consultant to 89bio, Aardvark Therapeutics, Altimmune, Alnylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol Myers Squibb, CohBar, Eli Lilly, Galmed Pharmaceuticals, Gilead, Glympse Bio, Hightide, Inipharma, Intercept, Inventiva, Ionis, Janssen, Inc., Madrigal Pharmaceuticals, Merck, Metacrine, Inc., NGM Biopharmaceuticals, Novartis, Novo Nordisk, Pfizer, Sagimet Biosciences, Terns Pharmaceuticals, Theratechnologies and Viking Therapeutics. He has stock options in 89bio and Sagimet Biosciences. In addition, his institutions have received research grants from Arrowhead Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Galectin Therapeutics, Galmed Pharmaceuticals, Gilead, Hanmi, Intercept, Inventiva, Ionis, Janssen, Inc., Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Novo Nordisk, Pfizer, Sonic Incytes and Terns Pharmaceuticals. He is also the co-founder of LipoNexus, Inc. **PS** has received grant support and lecture fees from CSL Behring; grant support from Arrowhead Pharmaceuticals, Dicerna Pharmaceuticals and Vertex Pharmaceuticals; advisory board/consulting fees from BioMarin Pharmaceuticals, BridgeBio, GlaxoSmithKline, Intellia Pharmaceuticals and Takeda Pharmaceuticals.

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