Biomarkers Associated With Fibrosis Progression in Patients With Primary Sclerosing Cholangitis: an Ad Hoc Analysis from the PRIMIS Study

Poster 4317

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Conclusions

- In patients with PSC, higher baseline ALP and Ludwig fibrosis stage were associated with an increased risk of fibrosis progression
  - Higher baseline ALP levels were associated with a significantly greater risk of Ludwig fibrosis stage progression and increased LSM
  - Patients with F3 fibrosis (vs F0–2) at baseline had significantly greater increases in LSM and ELF score
- Our study also reveals the complexity of evaluating fibrosis progression using histological staging based on semi-quantitative ordinal parameters as endpoints in clinical trials, particularly in indications with heterogeneous fibrosis stages across biopsy sites
  - Fibrosis stages were heterogeneous: patients with F3 fibrosis at baseline had a significantly lower frequency of one-stage fibrosis increase than those with F0–2 fibrosis
  - Power calculations for histological fibrosis progression should be based on F0–3 individually

Plain Language Summary

- Liver stiffness, or fibrosis, is the main driver of disease worsening in patients with primary sclerosing cholangitis; however, risk factors for fibrosis worsening remain unknown
- In this study, we aimed to use data from a 96-week, phase 3 clinical trial to identify risk factors for fibrosis worsening
- We found that fibrosis worsening in patients with primary sclerosing cholangitis was more likely if they had higher levels of a liver enzyme called alkaline phosphatase, or more severe fibrosis, at the start of the study
- In conclusion, this study provides information on possible factors that may help us to determine if primary sclerosing cholangitis is likely to get worse

References: **1.** Karlsen TH, *et al. J Hepatol*. 2017;67:1298–323. **2.** Goode EC, *et al. Hepatology.* 2019;69: 2120–35. **3.** Loomba R, *et al. Gut.* 2022;72:581–9. **4.** Thorburn D, *et al. Hepatol Commun*. 2024;8:e0467.

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Introduction

- Primary sclerosing cholangitis (PSC) is a chronic, progressive liver disease characterized by biliary inflammation and fibrosis[1]
- PSC often progresses to cirrhosis, liver cancer, and other end-stage liver disease; however, patients with PSC are heterogeneous and the pathogenesis of PSC is poorly understood[1]
- There is no approved pharmacological treatment that can slow or halt the progression of PSC
- It is essential to be able to identify patients with PSC who have a high risk of disease progression in both clinical trials and in daily clinical practice[2]

Objectives

- To identify risk factors for fibrosis progression in patients with noncirrhotic PSC

Methods

- This was an ad hoc analysis of data from the phase 3, double-blind, randomized, placebo-controlled, multi-center PRIMIS trial (NCT03890120)
  - The PRIMIS clinical trial assessed the efficacy and safety of cilofexor, a selective, nonsteroidal farnesoid X receptor agonist, in patients with PSC
  - Eligible patients aged 18–75 years with noncirrhotic, large-duct PSC and fibrosis stage F0–3 (Ludwig classification) were randomized 2:1 to receive oral cilofexor 100 mg or placebo once daily for 96 weeks
  - Individuals with moderate to severely active inflammatory bowel disease (partial Mayo score > 4 or rectal bleeding subscore > 1 unless bleeding was due to perianal disease) were excluded at screening
- There was no significant difference between cilofexor and placebo groups in histological fibrosis progression or noninvasive biomarkers of fibrosis at week 96; therefore, these groups were combined for this ad hoc analysis (n = 419)
- Fibrosis progression from baseline to week 96 was defined and analyzed separately using the following criteria:
  - Increase in histological fibrosis by at least 1 stage (Ludwig classification)
  - Increase in liver stiffness measurement (LSM) by at least 20% using FibroScan vibration-controlled transient elastography (VCTE) (threshold based on previous association with disease progression in metabolic dysfunction-associated steatohepatitis,[3] and intra-patient variation observed in patients with PSC from PRIMIS [**Table 1**])
  - Increase in Enhanced Liver Fibrosis (ELF) score by at least 0.5 (threshold based on previous association with disease progression in patients with PSC[4])
- A multivariate logistic regression was used to assess associations between fibrosis progression and baseline characteristics, adjusting for baseline LSM, ELF score, ANALI score, and ursodeoxycholic acid (UDCA) use

Results

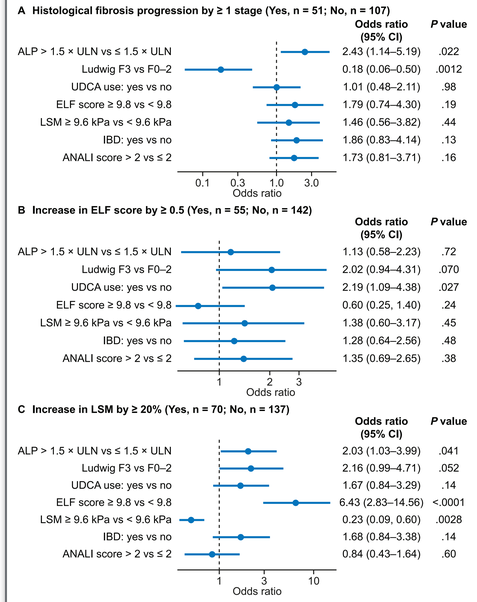
- Among patients with different baseline fibrosis stage, the intra-individual coefficient of variation for LSM was 20–35% (**Table 1**)
- Associations between baseline measures and risk of fibrosis progression at week 96 from the multivariate analysis are shown in **Figure 1**
  - Risk of histological fibrosis progression (≥ 1 stage) was significantly increased in patients with baseline alkaline phosphatase (ALP) levels > 1.5 × upper limit of normal (ULN) versus ≤ 1.5 × ULN, and significantly decreased in patients with F3 fibrosis versus F0–2
  - Risk of ELF score increase by at least 0.5 was significantly greater in patients taking UDCA at baseline compared with those who were not; this may have been due to lower liver enzyme levels in patients taking UDCA at baseline, among other imbalances in baseline characteristics between these subgroups (**Table 2**)
  - Risk of LSM progression (≥ 20%) was significantly increased in patients with ELF score ≥ 9.8 versus < 9.8 and (to a lesser extent) in patients with ALP > 1.5 × ULN versus ≤ 1.5 × ULN
- Patients with F3 fibrosis at baseline had significantly higher baseline LSM and ELF scores than those with F0–2 (**Table 2**), and greater increases in these noninvasive markers of fibrosis progression from baseline to week 96 (**Figure 2**)

Table 1. Intra-individual Coefficients of Variation for LSM by Ludwig Fibrosis Stage for the PRIMIS Study

Baseline Ludwig stage	n	Intra-patient CV, %
F0	25	25.1
F1	26	26.0
F2	27	20.3
F3	20	35.0
F0–2	78	23.6
All	98	29.3

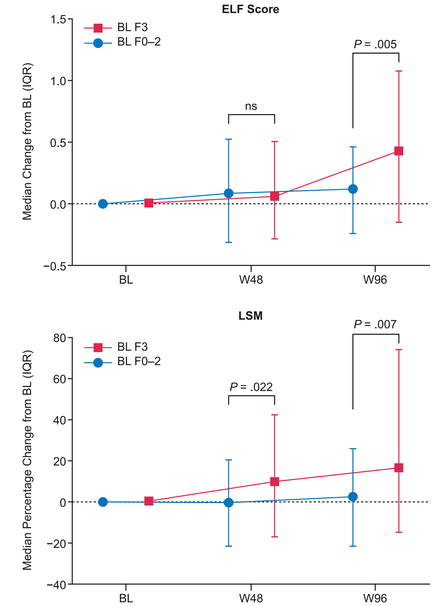
Intra-individual CVs for FibroScan LSM (kPa) were assessed using data collected at baseline, week 24, and week 48 in patients with available data at all visits and without clinical events by week 48 in the PRIMIS study. A random intercept model was fitted, assuming constant between- and within-patient variation over time. The intra-individual CV was calculated as the estimated within-patient standard deviation divided by the estimated mean.
CV, coefficient of variation; LSM, liver stiffness measurement.

Figure 1. Association of Baseline Biomarkers with Fibrosis Progression at Week 96 (Multivariate Analysis)



Odds ratios and *P* values were derived from the multivariate logistic regression.
ALP, alkaline phosphatase; ELF, Enhanced Liver Fibrosis; IBD, inflammatory bowel disease; LSM, liver stiffness measurement; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Figure 2. Change from BL in ELF Score and LSM by BL Fibrosis Stage



P values were calculated using the Wilcoxon rank-sum test.
BL, baseline; ELF, Enhanced Liver Fibrosis; IQR, interquartile range; LSM, liver stiffness measurement; ns, not significant; W, week.

Table 2. Baseline Characteristics for Subgroups Analyzed

	ALP		Ludwig		UDCA		ELF score		LSM		IBD		ANALI score	
	≤ 1.5 × ULN	> 1.5 × ULN	F0–2	F3	Yes	No	< 9.8	≥ 9.8	< 9.6 kPa	≥ 9.6 kPa	Yes	No	≤ 2	> 2
Ludwig F0–2, n (%)	189 (86%)	**122 (62%)***	NA	NA	176 (72%)	135 (79%)	254 (81%)	**55 (56%)***	241 (82%)	**45 (54%)***	216 (74%)	95 (77%)	191 (77%)	99 (70%)
UDCA, yes, n (%)	134 (61%)	112 (57%)	176 (57%)	70 (67%)	NA	NA	176 (56%)	**68 (69%)***	154 (52%)	**65 (77%)***	166 (57%)	80 (65%)	145 (59%)	83 (59%)
IBD, yes, n (%)	159 (73%)	133 (68%)	216 (69%)	76 (72%)	166 (67%)	126 (74%)	230 (73%)	**60 (61%)***	204 (69%)	59 (70%)	NA	NA	170 (69%)	99 (70%)
ANALI score	2 (1, 3)	**2 (2, 4)***	2 (1, 4)	2 (2, 4)	2 (2, 4)	2 (1.5, 4)	2 (2, 3)	**3 (2, 4)***	2 (1, 4)	**3 (2, 4)***	2 (2, 4)	2 (1,3)	NA	NA
LSM, kPa	5.9 (4.6, 7.9)	**8.2 (6.4, 10.3)***	6.4 (5.0, 8.7)	**9.2 (6.8, 11.8)***	7.4 (5.7, 10.3)	**6.4 (4.7, 8.6)***	6.4 (5.0, 8.5)	**9.2 (6.8, 12.6)***	NA	NA	7.0 (5.3, 9.2)	7.1 (5.3, 9.4)	6.4 (5.0, 8.5)	**8.1 (6.1, 10.4)***
ELF score	8.7 (8.2, 9.2)	**9.5 (8.9, 10.1)***	8.9 (8.3, 9.5)	**9.6 (8.9, 10.2)***	9.2 (8.5, 9.9)	8.9 (8.4, 9.5)	NA	NA	8.9 (8.3, 9.4)	**9.9 (9.2, 10.5)***	9.0 (8.4, 9.6)	9.2 (8.5, 10.0)	8.9 (8.3, 9.5)	**9.3 (8.7, 10.1)***
ALP, U/L	NA	NA	150 (98, 231)	**290 (174, 437)***	173 (110, 272)	182 (104, 317)	150 (98, 222)	**333 (174, 482)***	159 (104, 243)	**268 (161, 425)***	170 (104, 293)	183 (116, 297)	156 (98, 271)	**190 (128, 344)***
AST, U/L	27 (22, 36)	**61 (43, 86)***	33 (24, 55)	**57 (40, 84)***	35 (24, 56)	**47 (28, 75)***	33 (25, 51)	**63 (39, 90)***	35 (25, 57)	**58 (38, 82)***	39 (26, 65)	37 (24, 62)	36 (24, 63)	**43 (27, 74)***
ALT, U/L	30 (20, 50)	**88 (54, 121)***	40 (25, 72)	**82 (48, 119)***	44 (24, 74)	**61 (31, 107)***	42 (25, 70)	**91 (41, 121)***	44 (26, 75)	**83 (49, 108)***	49 (27, 94)	50 (24, 93)	46 (25, 94)	57 (28, 104)
GGT, U/L	64 (30, 143)	**321 (174, 597)***	112 (44, 251)	**305 (145, 540)***	125 (50, 270)	**228 (74, 494)***	124 (46, 251)	**302 (125, 537)***	134 (51, 298)	**289 (124, 503)***	146 (55, 342)	148 (58, 347)	125 (43, 322)	**189 (79, 429)***

Data are median (IQR) unless otherwise specified. Patient numbers associated with each comparison are available as supplementary material accessible via the QR code.
Bolded text with superscript asterisk indicates significant (*P* < .05) difference for baseline characteristic between the analyzed subgroups. *P* values were derived from Wilcoxon rank-sum test for continuous parameters, and Pearson's Chi-squared test for categorical parameters.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ELF, enhanced liver fibrosis; GGT, gamma-glutamyl transferase; IBD, inflammatory bowel disease; IQR, interquartile range; LSM, liver stiffness measurement; NA, not applicable; UDCA, ursodeoxycholic acid.

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