FRI-033

Long-Term Obeticholic Acid Treatment is Associated With Improvements in Collagen Morphometry in Patients With Primary Biliary Cholangitis

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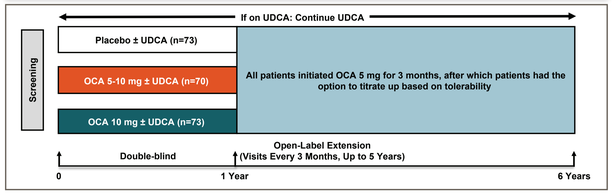
Introduction

- Primary biliary cholangitis (PBC) is a rare autoimmune liver disease of the intrahepatic bile ducts, leading to progressive fibrosis and eventual cirrhosis[1]
- In patients with PBC, cirrhosis-related events and clinical outcomes have been associated with the fibrosis stage[2-4]
- Measuring collagen content is emerging as a reliable method of quantifying liver fibrosis[5] and has shown evidence of being an effective tool in patients with PBC[6]
- Second harmonic generation (SHG) microscopy is a new tissue imaging technology that allows the accurate quantification of several collagen parameters on unstained tissue sections[7]
- Obeticholic acid (OCA) is a selective, potent farnesoid X receptor (FXR) agonist approved as a second line therapy in patients with PBC and an inadequate response to or intolerance of ursodeoxycholic acid (UDCA)[8]
  - Approval is based on a surrogate endpoint of biochemistry (alkaline phosphatase [ALP] and bilirubin)

Objective

- This post-hoc analysis assessed the impact of 3 years of OCA treatment on collagen morphometry using biopsy samples from the PBC OCA International Study of Efficacy (POISE) study

Methods



STUDY DESIGN:

- POISE was a randomized, double-blind, placebo-controlled, pivotal Phase 3 study evaluating OCA treatment in 216 patients with PBC through a 12-month double-blind (DB) phase and 5-year open-label extension (OLE) phase[8]
- POISE included a prespecified substudy that evaluated biopsy samples at baseline (up to 1 year prior to the start of the DB phase) and after approximately 3 years of OCA treatment

POST-HOC ANALYSIS:

- For patients that had paired evaluations (both baseline and on-treatment) biopsies underwent:
  - Nakanuma scoring[9] by 2 liver pathologists in a consensual reading, blinded to randomization and timing of biopsies
  - Collagen quantification by second harmonic generation (SHG) and 2-photon excitation (2PE) microscopy on unstained slides
    - Collagen area ratio (CAR): area of collagen (collagen pixel count) / total area of region of interest (total pixel count)
    - Collagen fiber density (CFD): total "brightness" of collagen (intensity) / collagen surface area
    - Collagen reticulation index (CRI): measure of complexity of collagen network (collagen branch points / collagen length)
    - Fibrosis composite score (FCS): composed of 15 unique morphometric parameters

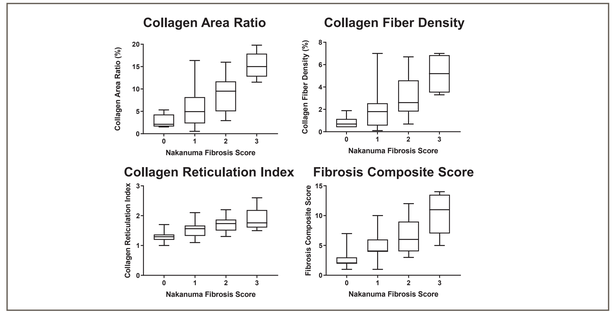
Results

Table 1. Baseline characteristics

Characteristic	OCA All Biopsy Population (N=30)	OCA Paired Collagen Population (N=16)
Age, years	55.9 (10.1)	58.9 (7.9)
Female, n (%)	27 (90)	15 (94)
White, n (%)	28 (93)	14 (88)
Body Mass Index, kg/m²	27.9 (4.9)	28.9 (4.3)
Alkaline Phosphatase, U/L	332.2 (97.4)	325.2 (116.6)
Total Bilirubin, mg/dL	0.6 (0.4)	0.5 (0.3)
Direct Bilirubin, mg/dL	0.3 (0.4)	0.2 (0.2)
Alanine Aminotransferase, U/L	61.1 (40.6)	50.6 (19.9)
Aspartate Aminotransferase, U/L	56.4 (30.3)	50.7 (24.6)
Gamma Glutamyl Transferase, U/L	226.5 (142.6)	176.9 (114.7)
Use of UDCA, n (%)	29 (97)	16 (100)
Daily Dose of UDCA, mg/kg	15.1 (3.4)	14.1 (2.6)

Data are mean (standard deviation) unless otherwise indicated.
[a]17 patients had adequate paired biopsies used for evaluation of Nakanuma score; 16 of these patients had adequate paired biopsies and unstained slides for evaluation of collagen by second harmonic generation/2-photon excitation microscopy.
OCA, obeticholic acid; UDCA, ursodeoxycholic acid.

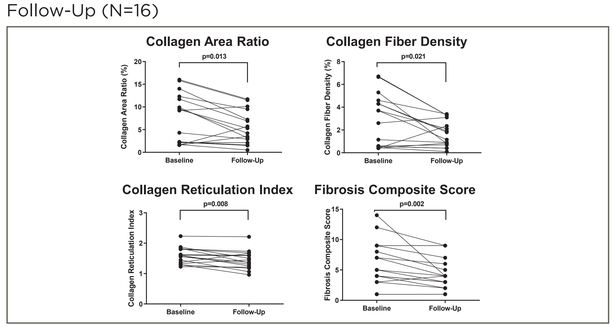
Figure 1. Collagen Morphometry vs Nakanuma Fibrosis Score (N=30 subjects, 46 slides)



Line within box represents median; top and bottom of box represent IQR; bars represent min and max.

- In the all biopsy population (N=30), the CAR, CFD, CRI, and FCS all increased in parallel with the Nakanuma fibrosis score

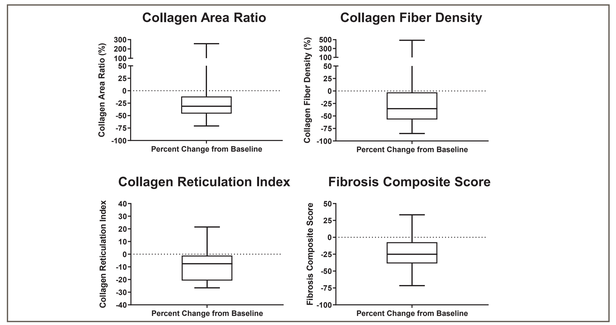
Figure 2. Individual Patient Collagen Morphometry From Baseline to Follow-Up (N=16)



p-value obtained using Wilcoxon Signed Rank test.

- OCA treatment resulted in significant reductions from baseline in the median (Q1, Q3) CAR (-2.1 [-4.6, -0.3], p=0.013), CFD (-0.8 [-2.5, 0.0], p=0.021), CRI (-0.1 [-0.3, 0.0], p=0.008), and FCS (-1.0 [-2.5, -0.5], p=0.002)

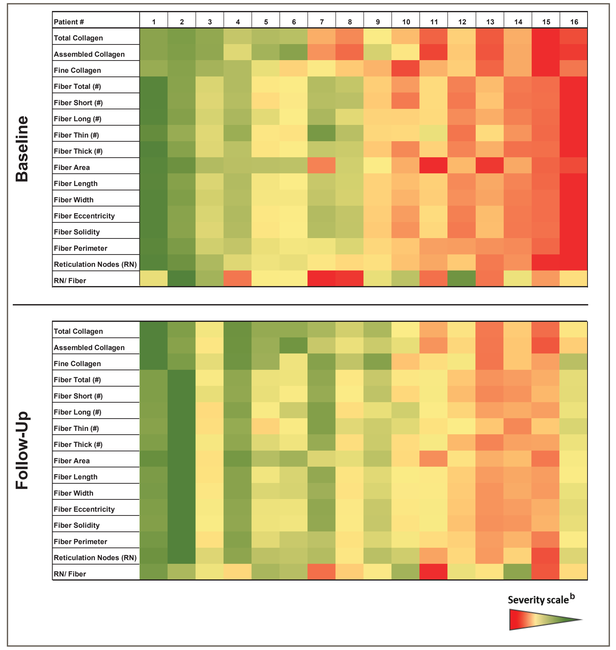
Figure 3. Percent Change From Baseline in Collagen Morphometry and the Fibrosis Composite Score (N=16)



Line within box represents median; top and bottom of box represent IQR; bars represent min and max.

- Reductions represent -31%, -35%, -7%, and -25% percent change from baseline in CAR, CFD, CRI, and FCS, respectively

Figure 4. Collagen Morphometry Heat Map (N=16)[a]



[a]Each row corresponds to individual collagen morphometric parameters; each column corresponds to individual patient reads.
[b]Colorimetric scale displays shades of colors ranging from red (most severe fibrosis) to yellow to green (least severe fibrosis).

- OCA treatment resulted in an improvement in most collagen parameters in most patients as observed qualitatively by a reduction in red and increase in green within the heat map at the follow-up biopsy relative to baseline

Table 2. Cumulative Safety Across 3 Years of OCA Treatment

Adverse Events	Total OCA N=16
Pruritus	11 (69)
Fatigue	8 (50)
Arthralgia	5 (31)
Upper respiratory tract infection	4 (25)
Diarrhea	4 (25)
Nasopharyngitis	4 (25)
Urinary tract infection	4 (25)
Pain in extremity	4 (25)
Influenza	4 (25)

Adverse events occurring in >3 patients while receiving OCA.
Data are n (%).
OCA, obeticholic acid.

- All serious adverse events were considered unlikely or not related to OCA

Conclusions

- The majority of patients with PBC receiving 3 years of OCA treatment in this study showed improvements or stabilization in collagen morphometry
- Significant reductions were observed in collagen area ratio, collagen fiber density, and collagen reticulation index as assessed by SHG/2PE microscopy
- Morphometric measures of fibrosis increased with increasing histologic disease severity as assessed by the Nakanuma fibrosis score, supporting the potential validity of collagen measurements by SHG/2PE
- The data from this POISE subgroup analysis support that in patients with an inadequate response to UDCA, 3 years of OCA treatment results in an improvement or stabilization in fibrosis progression

References

1. Tan D and Goodman ZD. *Clin Liver Dis*. 2018; 22:579-588.
2. Kumagi T, et al. *Am J Gastroenterol*. 2010;105(10):2186-94.
3. Kakuda Y, et al. *Human Pathology*. 2013;44(6)1107-1117.
4. Namisaki T, et al. *Hepatol Res*. 47: E178–E186.
5. Almpanis Z, et al. *Ann Gastroenterol*. 2016;29(4):445-453.
6. Stasi C, et al. *Dig Liver Dis*. 2016;48(3):298-301.
7. Chang PE, et al. *PLoS One*. 2018;13(6):e0199166.
8. Nevens F, et al. *N Eng J Med*. 2016;375:631-643.
9. Nakanuma Y, et al. *Pathology International*. 2010;60:167-174.

Disclosure

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Clinical Trial Information: CT.gov: NCT01473524; Eudra CT: 2011-004728-36

Intercept

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