Clinics and Research in Hepatology and Gastroenterology (2019) 43, e33—e36

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

LETTER TO THE EDITOR

Use of Fenofibrate for patients with primary Sclerosing Cholangitis

Dear editor,

It is with great interest we read the article titled ''Primary sclerosing cholangitis response to the combination of fibrates with ursodeoxycholic acid: French-Spanish experience'' by Lemoinne and colleagues [1]. We would like to share our experience and report the results of a pilot study we performed to evaluate the efficacy of fibrates on primary sclerosing cholangitis (PSC).

Data available from multiple studies support the use of fibric acid derivatives in patients with primary biliary cholangitis, another cholestatic liver disease, with consistent biochemical improvement in treated patients [2,3]. Until the study by Lemoinne et al. [1],promising experience with fibric acid derivatives in PSC had been demonstrated only in case reports and small case series describing rapid decline in serum alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT) and transaminases upon start of bezafibrate for patients with well documented PSC [4—9].

We therefore performed an uncontrolled, prospective, open label pilot study to evaluate the safety and efficacy of 160 mg fenofibrate (provided as Triglide, by Shionogi Inc.) given daily for 6 months in patients with PSC. The study was approved by the institutional review boards of both the University of Florida and the University of Miami, and adhered to the tenants of the Declaration of Helsinki. Informed consent was obtained from all subjects. Patients 18 to 75 years of age with a confirmed diagnosis of large duct PSC and whose serum alkaline phosphatase levels were elevated to at least 1.5 times the upper limit of normal were included. Exclusion criteria included pregnant or nursing women, anticipated need for liver transplantation in one year, recipients of liver transplantation, recurrent variceal hemorrhage, uncontrolled encephalopathy or refractory ascites, acute or chronic renal failure, defined as GFR < 60 mL/min, known cholecystitis, current use of coumadin anticoagulation therapy or statins, and previous history of, or known high risk for, venous thromboembolism.

A complete history and physical exam were performed prior to study enrollment. FibroScan (Echosens, Paris, France) was performed to measure liver stiffness both at entry and at the end of the study. Fenofibrate (Triglide, First Horizon, GA, US) 160 mg/day was given to all subjects once daily for the duration of the study. Baseline and monthly blood tests for serum ALP, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, and creatinine were measured. Prothrombin time and International Normalized Ratio (PT/INR), as well as a complete blood count (CBC) were measured at baseline, 3 months, and study exit. Patients were contacted monthly to discuss new symptoms and adverse events. The primary endpoint was change in serum ALP. We planned to enroll 20 patients; however, study was terminated early after a 1-year enrollment period due to slow recruitment and lack of funding. Descriptive statistics are expressed as medians [range]. Continuous variables were analyzed using Wilcoxon matched pairs test.

Eight patients were enrolled, 7 (87.5%) were male, 7 White, and the median age at entry was 41 years-old. Six patients had associated inflammatory bowel disease, five ulcerative colitis and one Crohn's disease. Three patients were on UDCA 1—1.5 g/day. All subjects completed the study. Matched pair analysis of the 8 subjects showed that ALP decreased significantly at 6 months compared to baseline levels [290 (216, 850) vs. 165.5 (104, 273) IU/L, $P = 0.02$] (Fig. 1). The median decrease was 47% (range 21—70%). ALT improved from 108 (40, 205) to 75 (34, 119) IU/L, $P = 0.04$. Fig. 2 and 3 illustrate the trajectory of AST and ALT during the study. There was no statistically significant change in serum total bilirubin, AST, prothrombin time or albumin. Table 1 summarizes changes in the biochemical markers at base line and end of study. One subject had worsening of total bilirubin during the study. The patient required endoscopic retrograde cholangiopacreatography (ERCP) with removal of biliary sludge, and bilirubin returned to baseline values. This patient did not meet criteria for study withdrawal and completed participation in the trial. He had more severe liver disease at entry, and the clinical course was typical of that of patients with PSC. However, given the small number of patients in this study, we cannot rule out the possibility that the study drug caused temporary worsening of his disease. Of note, at 9 weeks after study termination, median ALP increased from 165 (104,273) to 308 (143,670), $P = 0.008$, indicating a rebound effect after fenofibrate discontinuation.

https://doi.org/10.1016/j.clinre.2018.11.017

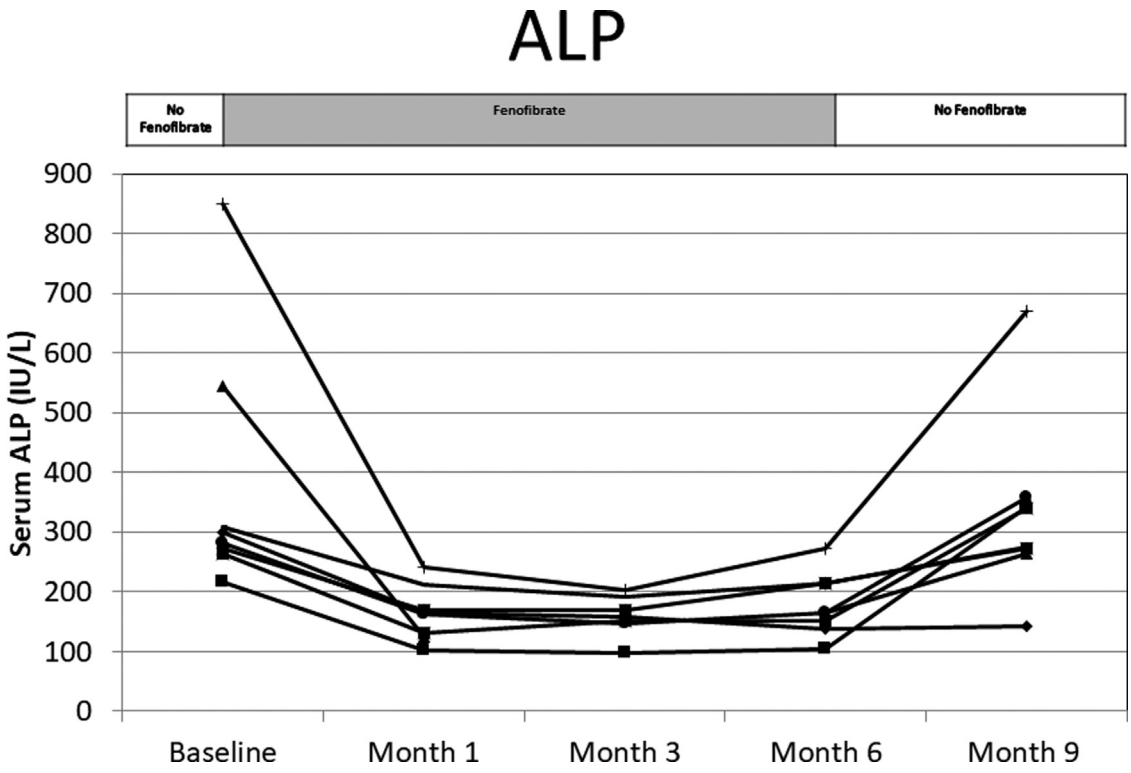

Figure 1 Spaghetti plots illustrating trajectory of serum alkaline phosphatase during the study.

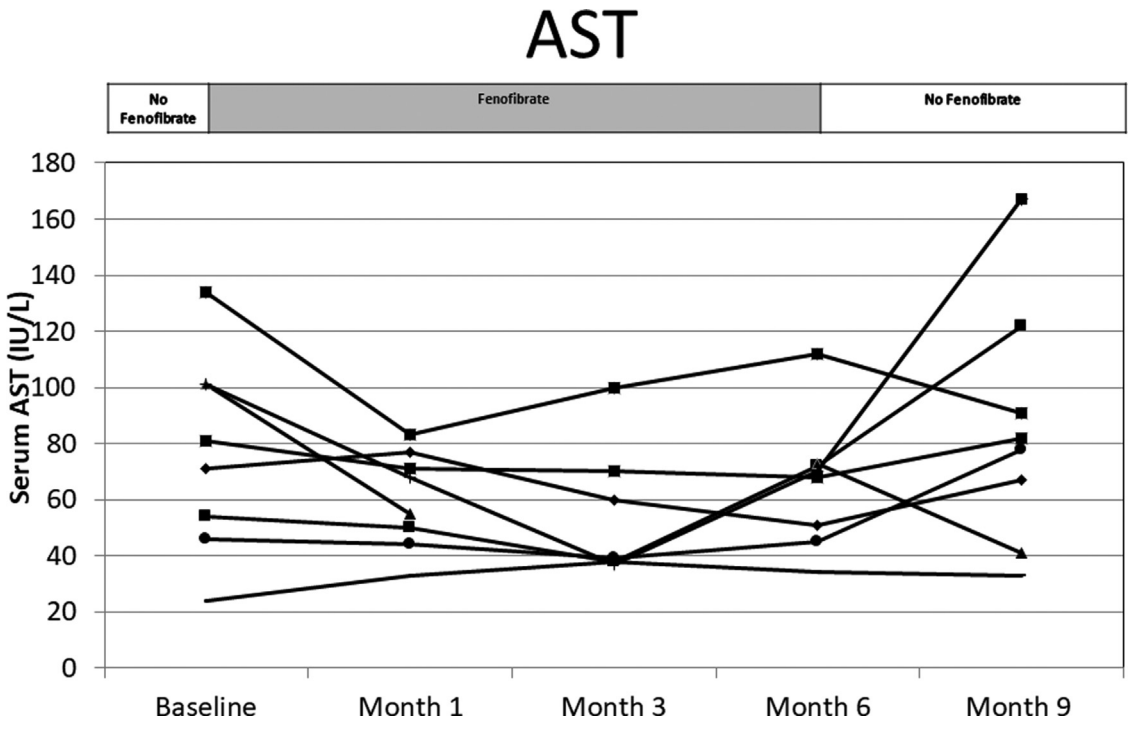

Figure 2 Spaghetti plots illustrating trajectory of serum aspartate aminotransferase during the study.

Only 4 subjects had liver elastography measured by FibroScan at baseline and end of study. Mild decrease in median liver stiffness was observed (12.9 (7.4, 16.9) vs. 9.55 (6.8, 17.6) kPa, $P = 0.64$). The lack of statistical significance can possibly be explained by the small number of patients. The only adverse event was worsening of psoriasis in one study participant. We observed mild increase in serum creatinine (0.89 vs. 1.0, $P = 0.01$) and a decrease in hemoglobin

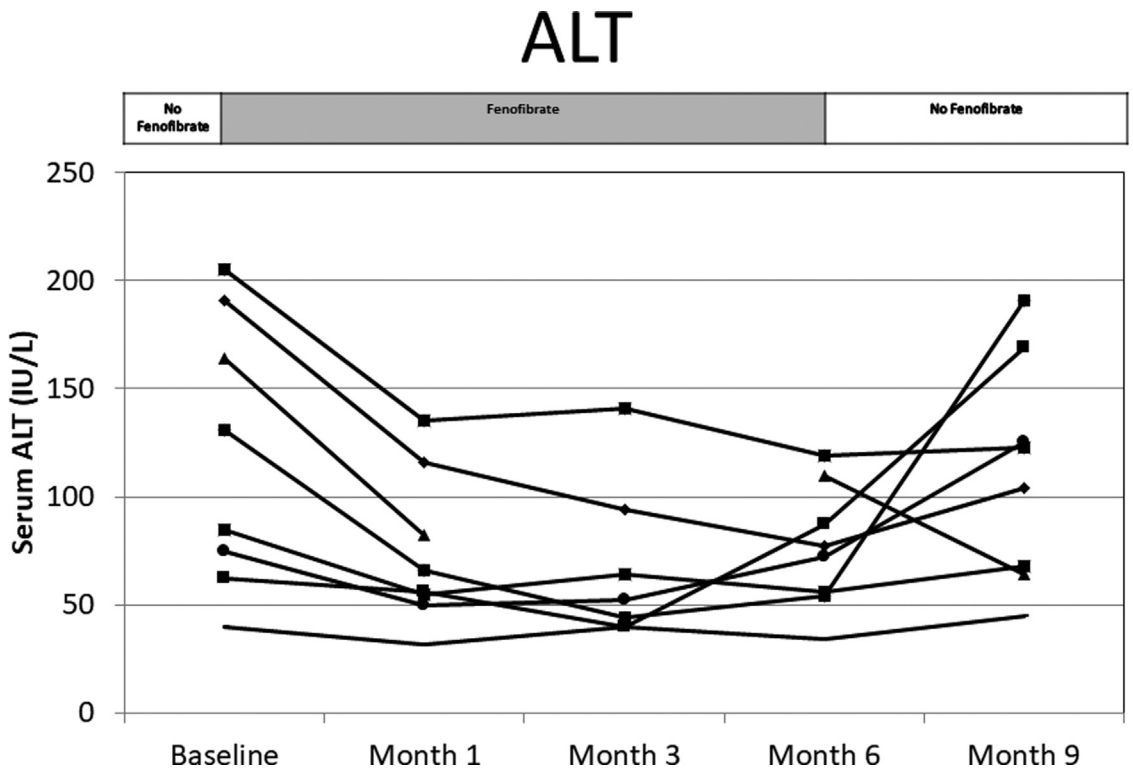

Figure 3 Spaghetti plots illustrating trajectory of serum alanine aminotransferase during the study.

Table 1 Changes in liver biochemistries from baseline to end of study.

	Baseline	Month 6	*P*-value
Alkaline phosphatase (IU/L)	290.5 (216, 850)	165.5 (104, 273)	0.02
Total bilirubin (mg/dL)	0.8 (0.6, 2.7)	0.7 (0.4, 4.2)	0.91
Aspartate aminotransferase (IU/L)	76 (24,134)	69 (34, 112)	0.13
Alanine aminotransferase (IU/L)	108 (40, 205)	74.5 (34, 119)	0.04
Prothrombin time (sec)	11.3 (10.4,14.1)	11 (10.2, 11.7)	0.15
Albumin (g/dL)	4.3 (3.9, 4.6)	4.4 (3.8, 4.6)	0.90

Results expressed as median (range). *P*-value obtained through matched pairs analysis with Wilcoxon signed rank test.

levels (13.9 vs. 13.4, $P=0.03$), neither considered a clinically significant change. The drug was overall safe and well tolerated for the duration of the study.

Our results suggest fibric acid derivatives can improve biochemical markers in patients with PSC, which is in agreement with findings of Lemoinne and colleagues. We agree establishing safety and efficacy of these agents in PSC should be the subject of further scientific inquiry.

Sincerely,

Sherine M Abdalla
Adriana Dejman
Virginia Clark
Cynthia Levy

Funding

No external funding was received for this article.

Authors' contribution

Study concept and design: CL; study conduct: CL and VC; drafting of the manuscript: SMA; acquisition of data: AD, VC, CL; analysis and interpretation of data: SMA, AD, VC, CL.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgments

The authors are indebted to the participating patients and to our study coordinators, Mrs. Lauren Morelli and Mrs. Marianelli Vega.

References

[1] Lemoinne S, Pares A, Reig A, et al. Primary sclerosing cholangitis response to the combination of fibrates with ursodeoxycholic

acid: French-Spanish experience. Clin Res Hepatol Gastroenterol 2018.
[2] Levy C, Lindor KD. Editorial: itching to know: role of fibrates in PBC. Am J Gastroenterol 2018;113(1):56—7.
[3] Corpechot C, Chazouilleres O, Rousseau A, et al. A placebo-controlled trial of bezafibrate in primary biliary cholangitis. N Engl J Med 2018;378(23):2171—81.
[4] Gondoh K, Ono T, Miyakoda K, et al. Bezafibrate alone is an effective first-line therapy for primary sclerosing cholangitis: a case report. Nihon Shokakibyo Gakkai Zasshi 2006;103(6):643—9.
[5] Kita R, Kita-Sasai Y, Hanaoka I, et al. Beneficial effect of bezafibrate on primary sclerosing cholangitis (three case reports). Am J Gastroenterol 2002;97(7):1849—51.
[6] Kurihara T, Maeda A, Shigemoto M, et al. Efficacy of bezafibrate in a patient with primary sclerosing cholangitis. J Gastroenterol 2003;38(3):300—1.
[7] Mizuno S, Hirano K, Tada M, et al. Bezafibrate for the treatment of primary sclerosing cholangitis. J Gastroenterol 2010;45(7):758—62.
[8] Mizuno S, Hirano K, Isayama H, et al. Prospective study of bezafibrate for the treatment of primary sclerosing cholangitis. J Hepatobiliary Pancreat Sci 2015;22(10):766—70.
[9] Mizuno S, Isayama H, Hirano K, et al. Factors predictive of the efficacy of bezafibrate therapy in patients with primary sclerosing cholangitis. Hepatol Res 2017;47(11):1102—7.

Sherine M Abdalla
Adriana Dejman
Virginia Clark
Cynthia Levy*
Division of Hepatology, Department of Medicine, University of Miami, Jackson Medical Towers, 1500 NW, 12th avenue, Suite 1101, Miami, FL, USA

* Corresponding author at: Division of Hepatology, Department of Medicine, University of Miami, Jackson Medical Towers, 1500 NW, 12th avenue, Suite 1101, Miami, 33136 FL USA
E-mail address: clevy@med.miami.edu (C. Levy)

Available online 14 March 2019