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Efficacy, safety, and tolerability of seladelpar in patients with compensated liver cirrhosis due to primary biliary cholangitis (PBC): a pooled analysis of phase 2 and phase 3 studies

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PO-1758

Circulating Fn14 is associated with pathogenic TH17 polarization in children with sclerosing cholangitis and inflammatory bowel disease

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Background and aims: Sclerosing cholangitis (SC) including primary sclerosing cholangitis (PSC) and autoimmune sclerosing cholangitis (ASC) are highly associated with inflammatory bowel disease (IBD), most commonly ulcerative colitis (UC), and SC-IBD may represent a unique IBD phenotype. We previously reported Th17.1 polarization in liver tissue, using both liver RNAs-seq and multi-parameter immunofluorescence, to segregate with SC-IBD. In the present study, we aim to discover biomarkers that selectively segregate with SC-IBD.

Method: Circulating plasma proteins were assayed by Slow Off-rate Modified Aptamer (SOMAscan) technology on children in 2 separate cohorts of SC-IBD and healthy controls (HC) (A: SC-IBD = 17, mean age = 15.4 years, male = 10, UC = 8; HC = 13, mean age = 17.8 years, male = 7; B: SC-IBD = 11, mean age = 16.1 years, male = 9, UC = 8; HC = 8, mean age = 14.1 years, male = 3). Significantly differentially expressed proteins determined by Wilcoxon Rank Sum test and corrected using a false discovery rate of <5% in cohort A were validated in cohort B using logistic regression. Spearman rank order correlation was used to correlate significant circulating plasma proteins and liver biochemistries.

Results: Of 1305 circulating plasma proteins assayed, 215 proteins were nominally significant between SC-IBD and HC in cohort A. Pathways related to TH1 and TH2 cell differentiation, TNF, and IL-17 signaling pathways were upregulated in children with SC-IBD. Ten of these 215 proteins were validated in cohort B with increased concentrations of CXCL8, TIMP1, FGF23, FCGR3B, PIGR, SCARB2, TNFRSF1A and Fn14, while ACY1 and CTSD were the only proteins with decreased concentrations in SC-IBD compared to HC. SC-IBD had a 3.7-fold increase in Fn14 compared to HC, highest among all validated proteins (Table 1). Concentrations of circulating Fn14 correlated with AST (rs = 0.40, p = 0.03) and GGT (rs = 0.37, p = 0.04).

Table 1: Mean concentrations[†] of significantly differentially expressed circulating plasma proteins in children with SC-IBD compared to HC assayed by SOMAscan

Protein	HC	SC-IBD	Fold Change (SC-IBD/HC)	Corrected p value
Fn14	377	1398	3.71	<0.001
SCARB2	441	872	1.98	<0.001
PIGR	12040	18706	1.55	<0.001
TNFRSF1A	1423	1962	1.38	<0.001
CXCL8	2407	3229	1.34	<0.001
TIMP1	482	500	1.04	<0.001
FCGR3B	2225	2265	1.02	<0.001
ACY1	16734	16609	0.99	<0.001
CTSD	1462	1421	0.97	<0.001

[†]Concentrations of proteins expressed as relative fluorescent units (RFU) calibrated to a standard curve

Conclusion: Large scale plasma proteomic analysis discovered circulating Fn14 to segregate with pediatric SC-IBD and to correlate with biomarkers of SC liver disease. Fn14 was previously shown to promote TH17 polarization in autoimmune conditions like rheumatoid arthritis. The role of Fn14 in driving hepatic TH17.1 requires further investigations.

PO-1809

Efficacy, safety, and tolerability of seladelpar in patients with compensated liver cirrhosis due to primary biliary cholangitis (PBC): a pooled analysis of phase 2 and phase 3 studies

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Background and aims: Patients with PBC and compensated cirrhosis can progress to decompensation with its associated complications, liver transplantation or death. PBC patients with an incomplete response or intolerance to UDCA have an unmet need to slow disease progression. Seladelpar, a selective PPAR delta agonist, has shown potent anti-cholestatic and anti-pruritic activity in PBC studies. We now report a pooled analysis from two studies assessing the efficacy, safety, and tolerability of seladelpar in PBC patients with compensated cirrhosis.

Method: Eligible PBC patients with an inadequate response or intolerance to UDCA (ALP ≥1.67 × ULN) were enrolled into an open-label phase 2 study (EudraCT 2016-002996-91) or a placebo (Pbo)-controlled phase 3 study (EudraCT 2018-001171-20). Cirrhosis was diagnosed using liver biopsy, imaging tests, or liver elastography. Patients received oral Pbo, seladelpar 5 mg or 10 mg once daily + UDCA if tolerated. Efficacy analyses at 3 months included composite response (ALp <1.67 × ULN, ALP decrease of ≥15% and total bilirubin [TB] ≤ULN), ALP % change, ALP ≤ULN, and changes in liver function. Safety was assessed for 3 months.

Results: Of 384 enrolled patients, 53 had compensated cirrhosis (Child-Pugh A: Pbo [n = 7], 5 mg [n = 22], and 10 mg [n = 24]). Baseline characteristics included: 92% female, mean age 58 yrs, 94%

on UDCA, ALP 287 U/L, TB 0.92 mg/dL, ALT 50 U/L, AST 49 U/L, GGT 228 U/L, albumin 3.96 g/dL, and platelets 197×10^3/μL. After 3 months, 39 patients were treated. The composite end point was met in 50% (9/18) of 5 mg and 63% (10/16) of 10 mg groups compared to none in Pbo (0/5). Reductions in ALP in the 5 mg (-31%, – 82 U/L) and 10 mg groups (–41%, –114 U/L) were greater than Pbo (–2.6%, –8.7 U/L). ALP was normalized in 3 patients in each seladelpar group (17–19%) but none in Pbo. Changes in ALT were –15%, –6%, and –32% in Pbo, 5 and 10 mg groups, respectively. Total bilirubin, platelets, albumin, and INR remained stable. One patient in 10 mg discontinued due to AE (pruritus). Three patients had an SAE: 2 on 5 mg (febrile neutropenia, procedural pain) and 1 on 10 mg (angina pectoris), all unrelated to study drug. Efficacy, tolerability, and safety in patients with compensated cirrhosis were comparable to that of non-cirrhotic patients.

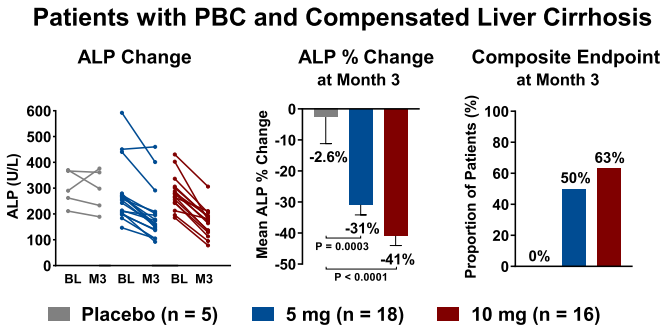

Figure:

Conclusion: Seladelpar appeared safe and was well tolerated and may provide an effective treatment option for patients with compensated liver cirrhosis due to PBC.

PO-1811

Odevixibat effects on cholestasis-related parameters: Analysis of pooled data from the PEDFIC 1 and PEDFIC 2 studies in children with progressive familial intrahepatic cholestasis

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Background and aims: Odevixibat, an ileal bile acid transporter inhibitor, is in development to treat cholestatic liver diseases. In the phase 3 PEDFIC 1 (P1) and PEDFIC 2 (P2) studies, odevixibat treatment reduced serum bile acids (sBAs) and improved pruritus in patients with progressive familial intrahepatic cholestasis (PFIC). Using pooled data from these studies, we analysed changes in parameters of cholestasis, pruritus, and hepatic laboratory markers and compared patients who responded to odevixibat treatment (Rs) with non-responders (NRs).

Method: P1 was a 24-week, randomized, placebo-controlled study in children with PFIC1 or PFIC2, and P2 is an ongoing, 72-week extension study in patients with any type of PFIC. In this pooled analysis, spanning 48 weeks, 77 patients have received odevixibat (PFIC1, n = 20; PFIC2, n = 51; PFIC3, n = 5; MYO5B deficiency, n = 1; overall median exposure: 37 weeks). Two responder definitions were examined: 1) sBA response (ie, sBAs <65 or <102 μmol/L for PFIC1 and PFIC2, respectively) and 2) sBA response *or* pruritus response (ie, a ≥1-point drop from baseline in PRUCISION score).

Results: Rates of sBA Rs and sBA or pruritus Rs were 31% and 57%, respectively, at weeks 0–24, 48% and 60% at weeks 25–36, and 59% and 65% at weeks 37–48. Among all odevixibat-treated patients, mean change from baseline (CFB) to week 48 in alanine aminotransferase (ALT) and total bilirubin was –82 U/L and –18 μmol/L, respectively. In general, Rs had greater mean CFB (ie, improvements) vs NRs in these hepatic laboratory parameters with long-term odevixibat treatment (Table) that started as early as week 4 and increased over time.

Table:

Liver Enzyme Levels	sBA Response				sBA or Pruritus Response			
	Yes		No		Yes		No	
	n (%[a])	Mean (SE)	m	Mean (SE)	n (%[a])	Mean (SE)	m	Mean (SE)
ALT, U/L								
Baseline	24 (39)	124 (33)	38	82 (12)	48 (63)	104 (18)	28	69 (11)
CFB→wk 4	23 (39)	–28 (37)	36	21 (16)	43 (61)	–2 (24)	27	9 (4)
CFB→wk 24	19 (40)	–67 (42)	28	–10 (11)	31 (62)	–56 (27)	19	5 (8)
CFB→wk 48	15 (63)	–112 (57)	9	–32 (22)	18 (75)	–108 (48)	6	–5 (15)
Total bilirubin, μmol/L								
Baseline	24 (39)	27 (7)	38	74 (12)	48 (63)	42 (6)	28	67 (16)
CFB→wk 4	23 (39)	–8 (4)	36	–10 (9)	43 (61)	–6 (4)	27	–14 (11)
CFB→wk 24	19 (40)	–23 (8)	28	–19 (10)	31 (62)	–19 (7)	19	–23 (13)
CFB→wk 48	15 (63)	–25 (11)	9	–6 (14)	18 (75)	–25 (9)	6	1 (20)

[a]Responder rate ([n/(n + m)] × 100).

Conclusion: Patients with PFIC who responded to odevixibat treatment had sustained improvements in cholestasis-related parameters that were not observed to the same extent in treatment non-responders.

PO-1828

Genetic mutation and cystic fibrosis-associated liver disease at the time of diagnosis in children: A correlational study

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Background and aims: It is estimated that 10 to 15% of patients with cystic fibrosis have liver disease (CFLD), this negatively impacts the evolution of the disease, it has been reported that dysfunction of the transmembrane conductance regulator (CFTR) has a direct effect on the cholangiocyte function, finally the spectrum of complications ranges from cholestasis, progressive fibrosis, biliary obstruction to focal biliary cirrhosis. Around 2000 mutations in CFTR have been determined and classified according to their functional defect, however, none of them have been associated with CFLD, accepting that this is due to the interaction of environmental factors,