AASLD Nov. 4-8, 2022

The Liver Meeting®

WASHINGTON D.C.

The Best of The Liver Meeting®

PEDIATRIC LIVER DISEASES

About the program:

Best of The Liver Meeting 2022 was created by the Scientific Program Committee for the benefit of AASLD members, attendees of the annual conference, and other clinicians involved in the treatment of liver diseases. The program is intended to highlight some of the key oral and poster presentations from the meeting and to provide insights from the authors themselves regarding implications for patient care and ongoing research.

Use of these slides:

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Exploring the genotype-phenotype relationship of variants of unknown significance in a genetic cholestasis panel

Objective

To determine which variants of unknown significance (VUS) are associated with progression of liver disease.

Methods

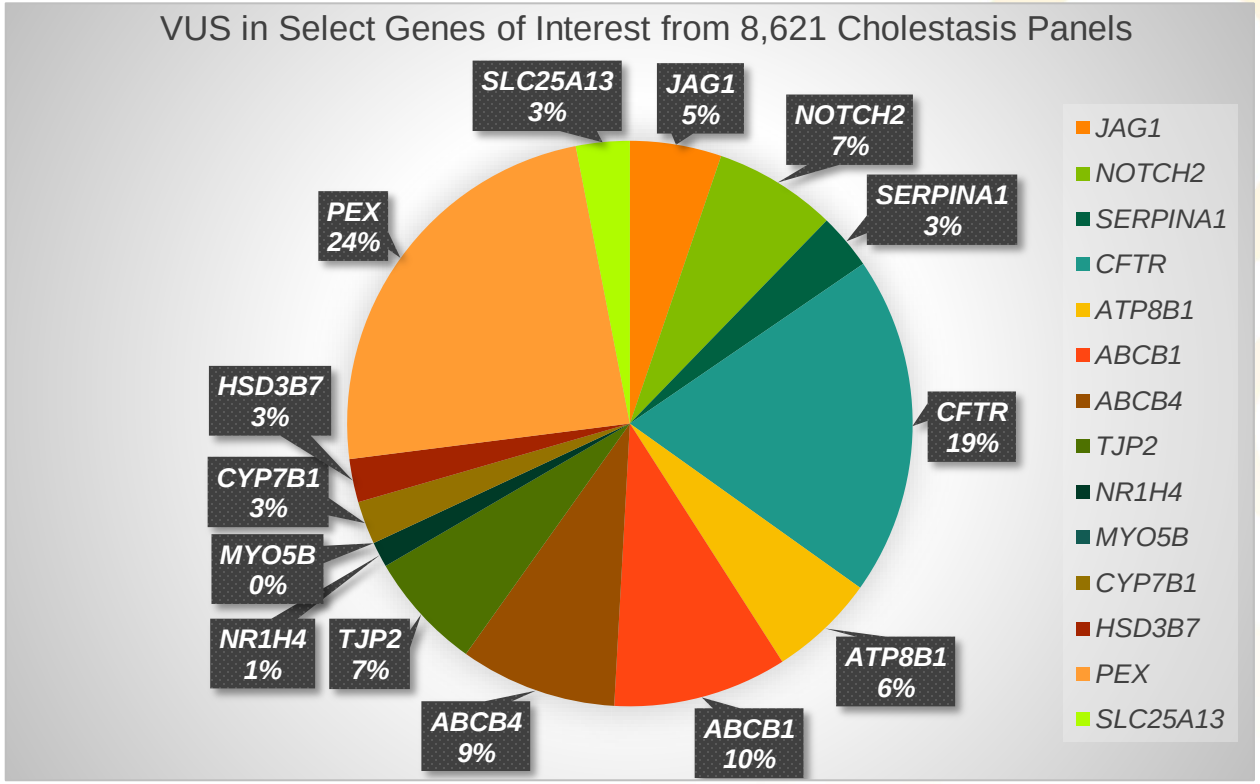
A multicenter non-concurrent prospective analysis and consortium in children with a VUS identified on a 77-gene cholestasis panel available through Prevention Genetics (previously EGL), from 2016 to present.

Main Findings

Of 8,621 cholestasis panels analyzed, 18,283 VUS were identified, including 6,384 in our 14 genes of interest. Normal results occurred in 1,665 tests (19%).

Conclusions

VUS were frequently identified on the panel. Our consortium is currently collaborating on a study to better determine the causal association of VUS to the development of the liver disease process.



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Hoskins B, et al., Abstract 15.

Distinct immune-metabolic signatures at diagnosis of BA are associated with future native liver survival

Aim

To identify immune-metabolic pathways at the time of biliary atresia (BA) diagnosis that are predictive of 2-year survival with native liver (SNL).

Methods

- Comparison of serum metabolites, serum cytokines, and hepatic immune cell subsets at time of diagnosis among BA patients and non-BA disease controls.
- Patient population: infants enrolled in the NIDDK-funded Childhood Liver Disease Research Network PROBE study.

Main Findings

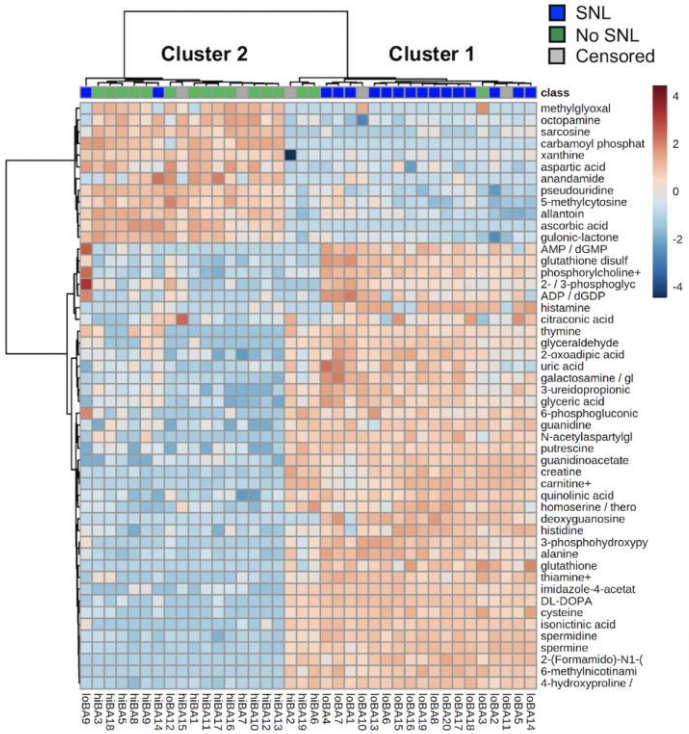
A. Hierarchical clustering of 260 metabolites in BA patients identified 2 distinct BA clusters that differed by future SNL status. **B.** Levels of the specific polyamine metabolites putrescine, spermidine, and spermine were increased in BA cluster 1. **C.** Serum GM-CSF and hepatic monocyte-like macrophages were also higher in BA cluster 1.

Conclusions

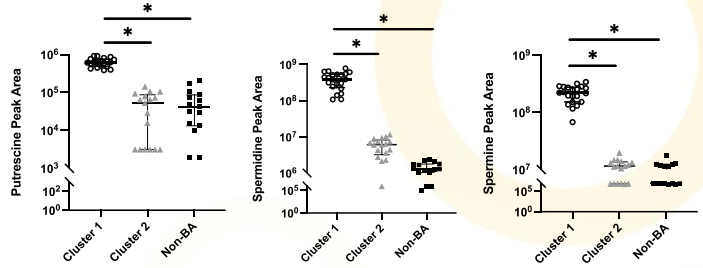
- Serum polyamine levels at diagnosis of BA are associated with differences in GM-CSF levels, hepatic monocyte-like macrophage numbers, and improved SNL.
- Polyamines are known to promote an anti-inflammatory immune response and may play a favorable in hepatic adaptation to biliary obstruction in BA.

Taylor S, et. al., Abstract 16.

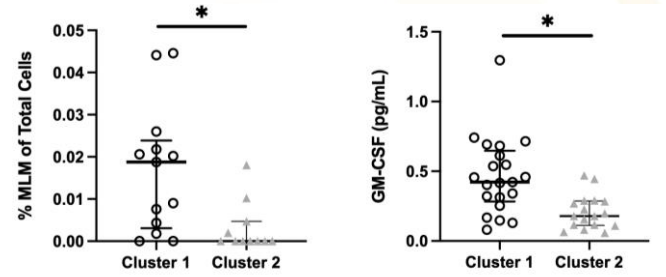
A. Overview of hierarchical clustering of serum metabolites in BA patients



B. Serum polyamines are significantly increased in BA cluster 1 with a higher rate of SNL



C. Increased hepatic monocyte-like macrophages (MLM) and serum GM-CSF are present in BA cluster 1



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Disease imprinting renders cholangiocytes susceptible to viral infection and proinflammatory phenotype in biliary atresia

Aim

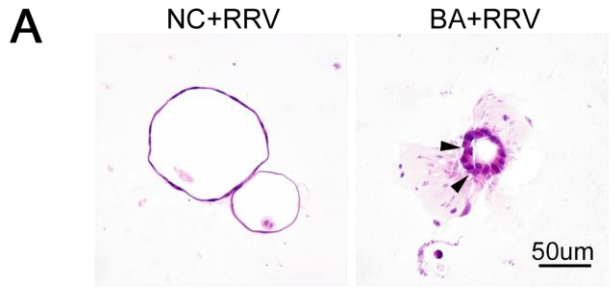
To investigate how diseased epithelium responds to proinflammatory stimuli using patient-derived cholangiocyte organoids in biliary atresia (BA).

Methods

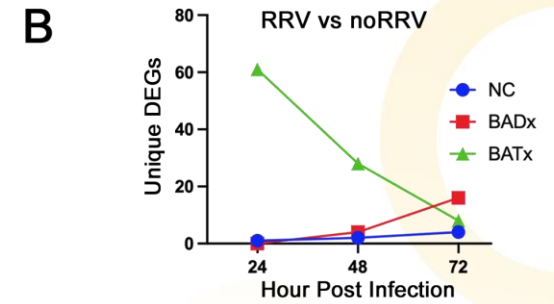
- Human cholangiocyte organoids (CO) derived from livers of normal donors (NC) and BA patients at diagnosis (BADx) and transplant (BATx) were subjected to rotavirus (RRV) infection. Gene expression was analyzed using RNA-seq. Transcription factors (TFs) were determined using TRRUST database.
- Mouse-COs were cocultured with murine macrophages (MΦ; Raw 264.7) 3h post LPS stimulation.

Conclusions

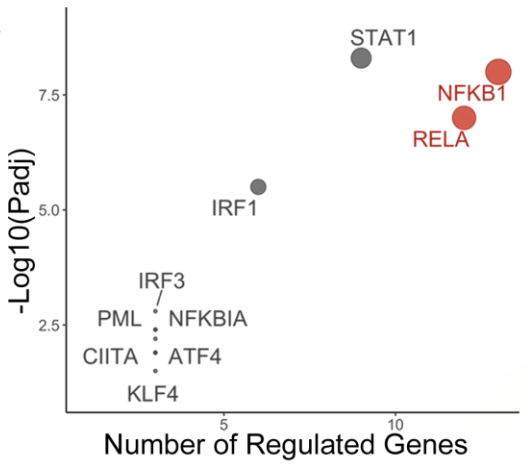
Cholangiocytes from BA patients have: 1) increased susceptibility to virus-induced injury, 2) intrinsic activation of NF-kB-related genes, and 3) ability to prolong macrophage proinflammatory phenotype.



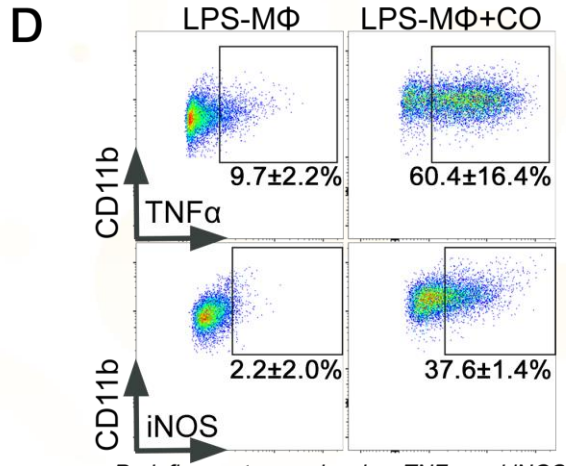
H&E staining of COs from NC and BA subjects 48h post RRV infection, showing severe injury in BA (arrowhead).



Number of unique differentially-expressed genes (DEGs) in RRV-infected COs compared to RRV-naive groups.



Transcription factors enriched from DEGs of RRV-infected BATx-COs show enriched NF-κB signatures.



Proinflammatory molecules, TNFa and iNOS, expressions are significantly enhanced in MΦ when cocultured with COs.

Li W, et al., Abstract 229.

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Accuracy of GDF15 and FGF21 to differentiate Mitochondrial Hepatopathies from other pediatric liver diseases

Objective

Our objective was to evaluate serum GDF15 and FGF21 as potential biomarkers to identify mitochondrial hepatopathies (MH) in children prospectively enrolled in NIH-funded longitudinal multicenter studies (ChiLDReN research network).

Methods

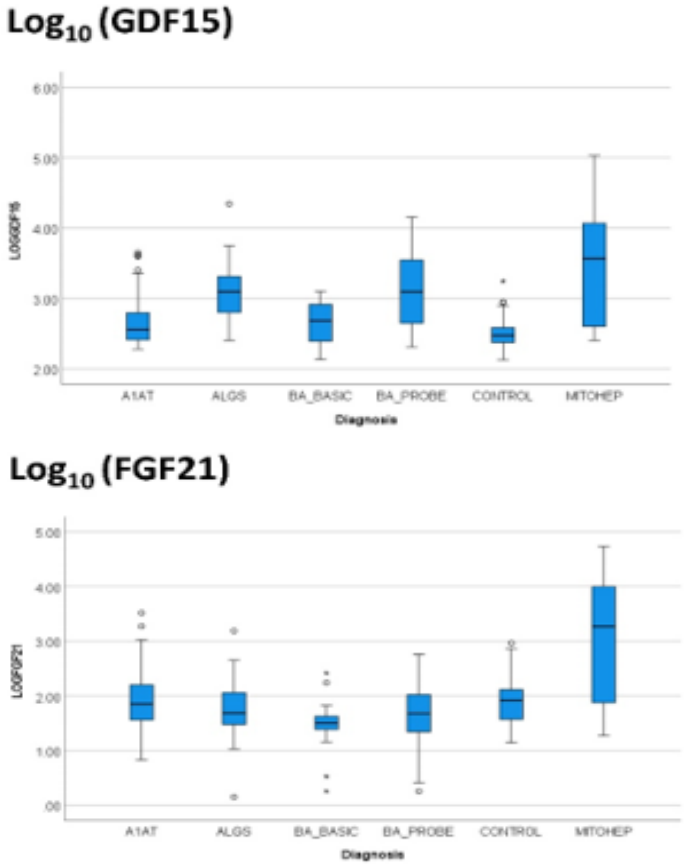
Participant population studied: 36 children with MH (17 with genetic dx) and age/sex matched children 38 each with biliary atresia (BA), α1-antitrypsin deficiency (A1AT), and Alagille syndrome (ALGS) and 200 normal controls.

Main Findings

GDF15 and FGF21 were elevated in MH compared to other groups (Figure). Elevation > 98%ile of both biomarkers was present in 94% MH with genetic dx (61% of all MH) vs. 3-11% of other liver diseases.

Conclusions

GDF15 and FGF21 are significantly higher in children with MH compared to other childhood chronic liver diseases, and markedly higher than controls. The finding of serum levels >98%ile for both biomarkers simultaneously is strongly suggestive of a MH.



Sokol R, et al., Abstract 230.

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Cidofovir usage in recent outbreak of adenovirus-associated acute liver failure in children: King's College Hospital experience

Hypothesis/Aim/Objective

We aimed to investigate the safety and efficacy of cidofovir in pediatric patients with adenovirus-associated acute liver failure (ALF).

Methods

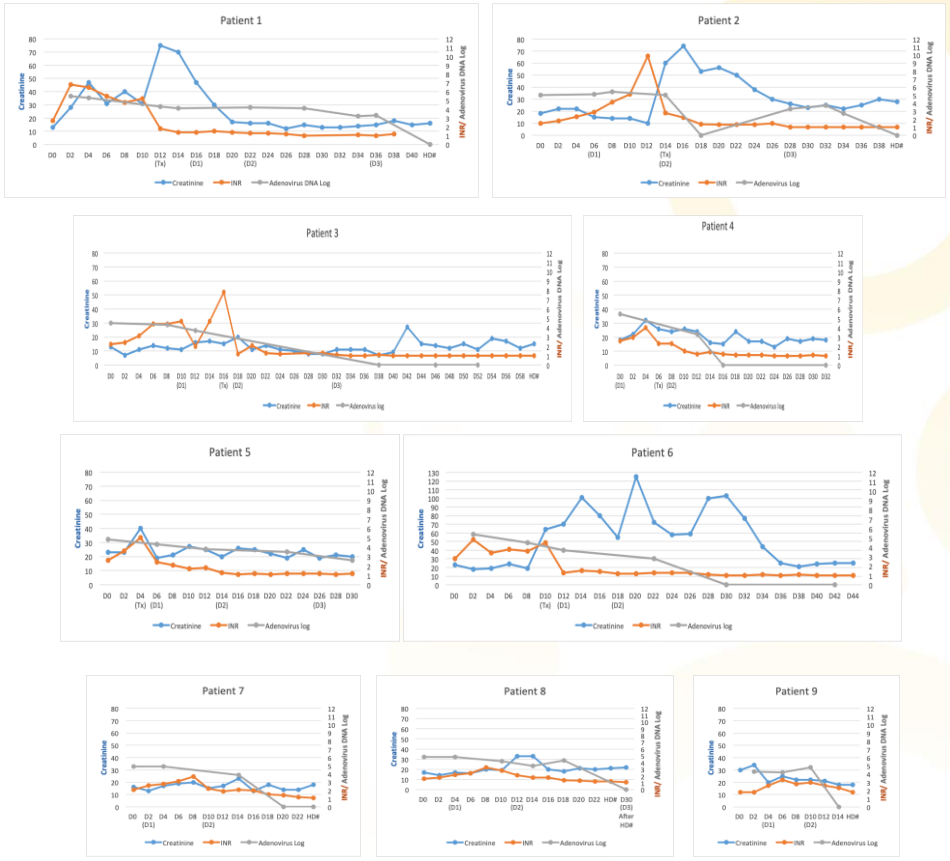
Retrospective cohort study of the use of cidofovir for adenovirus-associated ALF in children treated between January 2022 to May 2022 at King's College Hospital, United Kingdom.

- All patients received the standard dose of 5mg/kg weekly for two weeks then fortnightly, with hyperhydration.
- Patients who were admitted to the PICU were all neuroprotected.

Conclusions

Use of cidofovir in children with ALF and adenoviremia appears to be relatively safe and well-tolerated in the short-term with only transient nephropathy, and is effective in reducing adenoviremia.

All patients demonstrated biochemical and clnical response
4 patients had rise in creatinine after cidofovir, 1 had persistently raised creatinine 2 weeks after



Vimalesvaran S, et al., Abstract 237.

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A CRISPR screen in biliatresone-treated human cholangiocytes identifies HMMR as a modulator for biliary injury

Aims

To comprehensively identify genetic factors and pathways that alter cellular susceptibility to biliatresone, a toxin causatively linked to biliary atresia outbreaks in newborn Australian livestock.

Methods

A genome-wide pooled CRISPR-Cas9-mediated knockout screen was conducted in the presence and absence of biliatresone using H69, a normal cholangiocyte cell line. Functional validations of one of the gene hits were pursued using different liver cell types and zebrafish larvae.

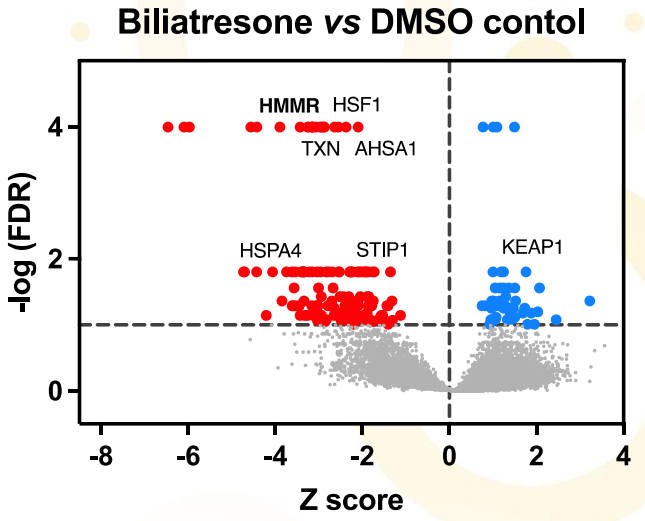
Main Findings

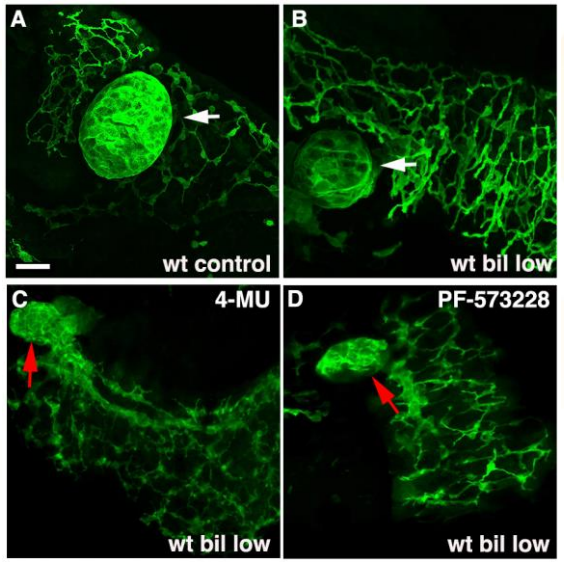
- We identified HMMR, a receptor for hyaluronic acid (HA), as one of the novel gene hits whose inactivation confers sensitivity to biliatresone.
- Functional validation studies showed that HMMR knockdown elicits cell-type specific phenotypes. Furthermore, suppression of HA synthesis (4-MU) and inhibition of FAK (PF-573228), a downstream effector of HMMR, sensitized extrahepatic cholangiocytes to low-dose biliatresone in the zebrafish larvae.
- The screen also identified genes involved in redox signaling and proteostasis, consistent with our prior studies and serve as an internal control for the screen.

Conclusions

Our study highlights the use of chemogenomic screens as an unbiased approach to uncover pathways modulating cellular responses to toxic insults and identify HMMR as a key regulator of cellular defense against biliatresone in bile duct cells.

Wu S-H, et al., Abstract 238.





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Worldwide outbreak of acute hepatitis in children: Interim results from the severe hepatitis in pediatric patients (SHIPP) international registry

Objective

Characterize the clinical characteristics, histology, and outcomes of pediatric patients with acute severe hepatitis.

Methods

Data was prospectively accrued by 26 sites on patients <18 yrs, with ALT>500, and no known chronic liver disease or acetaminophen ingestion.

Main Findings

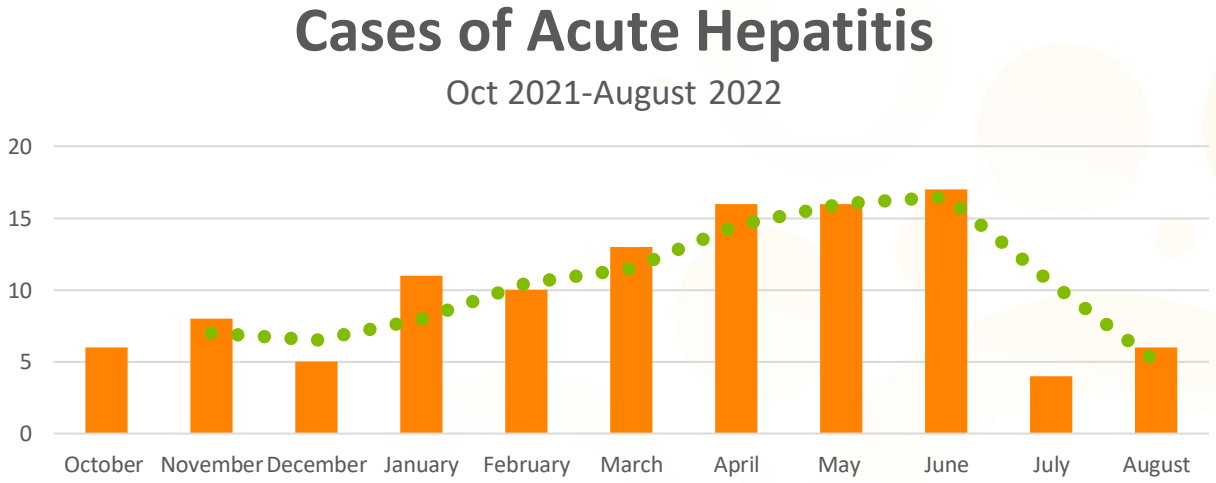
- 112 patients were reported.
- Adenovirus serum/whole blood DNA was detected in 17% and CMV and EBV serologies were positive in 6% and 16%, respectively.
- 44% had a positive respiratory panel test result with Rhino/Enterovirus being the most common (57%). Two patients each were positive for SARS-CoV-2 and Adenovirus.

Conclusions

- In a large multi-center dataset of pediatric patients with acute hepatitis, the majority did not have a singular definitive etiology but did recover spontaneously.
- Need for ongoing monitoring, data/sample collection, and future case-control studies.

	Median (IQR)
AST (IU/L)	2259 (747,3763)
ALT (IU/L)	1949 (934,3503)
Bili (mg/dL)	5.1 (1.5,11.4)
INR	1.4 (1.1,1.9)

Outcomes	N
Liver Transplantation	7
Mortality	2



Mohammad S, et al., Abstract LO0.

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Efficacy and safety of maralixibat in patients with progressive familial intrahepatic cholestasis (MARCH-PFIC): A randomized placebo-controlled phase 3 study

Methods

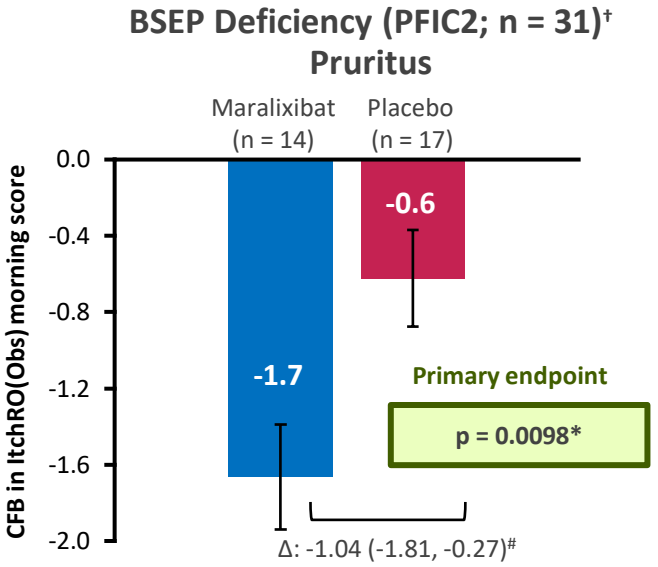
- 93 patients with PFIC and cholestatic pruritus were included: BSEP, FIC1, MDR3, TJP2, and MYO5B8 deficiencies as well as patients with previous surgery, variants not known, and heterozygous or truncated mutations.
- Patients were randomized (1:1) and treated for 26 weeks with maralixibat (570 µg/kg twice daily) or placebo.
- The primary efficacy endpoint was mean CFB to Week 26 in pruritus in participants with BSEP deficiency (n = 31).† Key secondary endpoints included: additional pruritus and sBA assessments in the BSEP deficiency and All-PFIC cohorts (n = 64).†
- Pruritus was measured by utilizing the ItchRO(Obs) 0-4 scale; ≥1 point reduction is clinically meaningful.

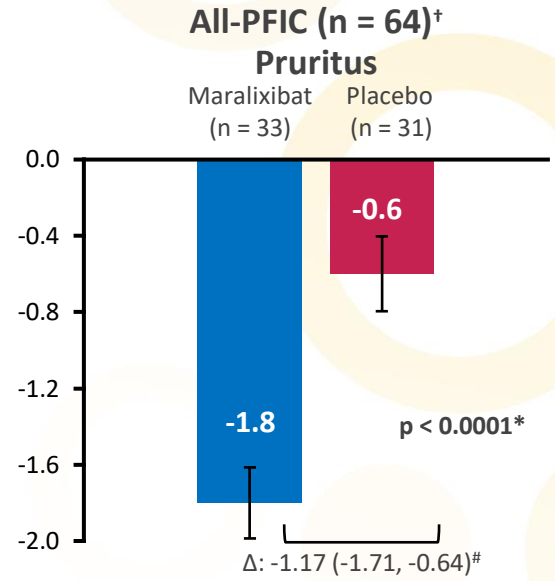
Main Findings

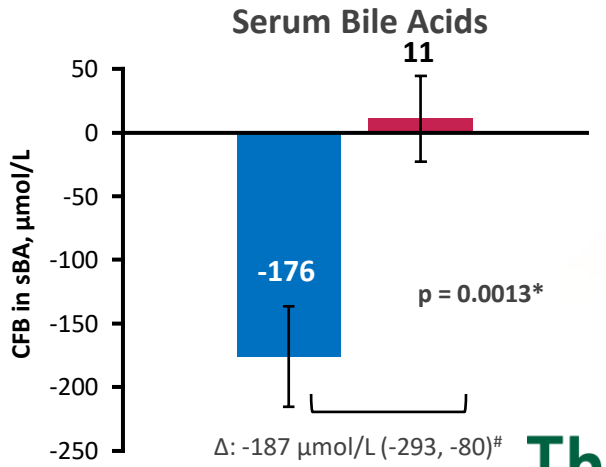
- **Efficacy:** The study met its primary and key secondary efficacy endpoints for the BSEP deficiency and All-PFIC cohorts (see figures).
- **Safety:** GI-related disorders were the most common TEAE, regardless of relatedness (57% maralixibat vs 20% placebo), mostly mild and transient (median duration 5.5 days). No severe cases of diarrhea. No deaths reported.

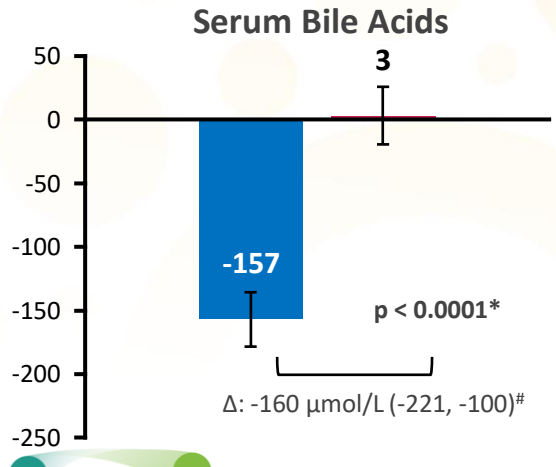
Conclusions

- This trial is the largest interventional study conducted in PFIC with an IBAT inhibitor including PFIC types that have not previously been studied.
- Statistically significant and clinically meaningful improvements in pruritus severity and sBA were observed in the BSEP deficiency and All-PFIC cohorts after maralixibat treatment.
- Treatment effect is greater than previously reported with lower doses.









*Comparison between maralixibat and placebo at Week 26.; †Biallelic mutations without truncated mutations or previous surgery.; #LS Mean Delta with 95% CI. Data are LS Mean with standard error bars. BSEP, bile salt export pump; IBAT, ileal bile acid transporter inhibitor; LS, least squares; PFIC, progressive familial intrahepatic cholestasis; nt, non-truncated; sBA, serum bile acids; t, truncated; TEAE, treatment emergent adverse events.

Miethke A, et al., Abstract LO1.

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Odevixibat treatment in responsive patients with BSEP deficiency restores biliary bile acid secretion

Objective

Evaluate sBA composition in patients with BSEP deficiency (ie, PFIC2) from PEDFIC 1, with odevixibat-treated patients categorized by sBA response (R) or nonresponse (NR).

Methods

- Patients with PFIC2 enrolled in the phase 3 PEDFIC 1 trial[1]
- sBA response: sBAs reduced ≥70% or levels ≤70 µmol/L
- sBA composition: measured by LC-MS/MS at week 24

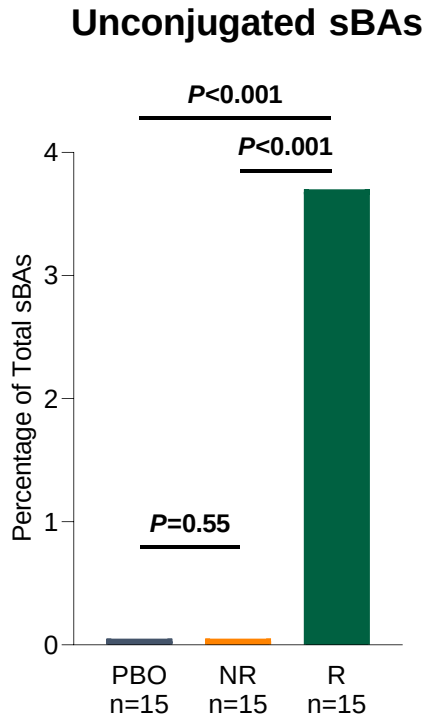
Main Findings

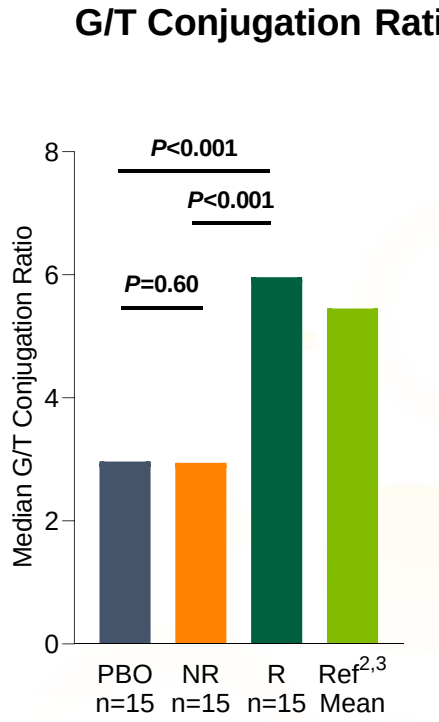
Versus nonresponders, responders (R) had

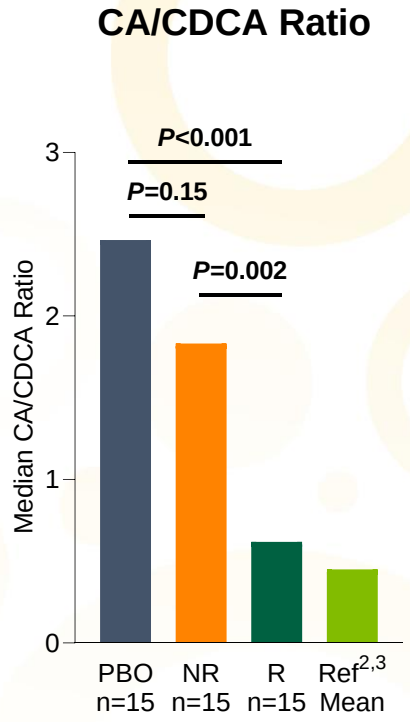
- No difference in secondary bile acids,
- ~70-fold increase in unconjugated sBAs (*left figure*),
- Increase in G/T conjugation ratio towards normal (*center figure*), and
- Decrease in CA/CDCA ratio towards normal (*right figure*).

Conclusion

Odevixibat restored biliary bile acid secretion in patients with PFIC2 who responded to treatment.







Nomden M, et al., Abstract LO4.

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Efficacy and safety of odevixibat in patients with Alagille syndrome: Top-line results from ASSERT, a phase 3, double-blind, randomized, placebo-controlled study

Objective

- Evaluate efficacy and safety of the IBAT inhibitor odevixibat in patients with Alagille syndrome

Methods

- ASSERT: 24-week, double-blind, randomized, placebo-controlled, multicenter, phase 3 study in children with Alagille syndrome

Main Findings

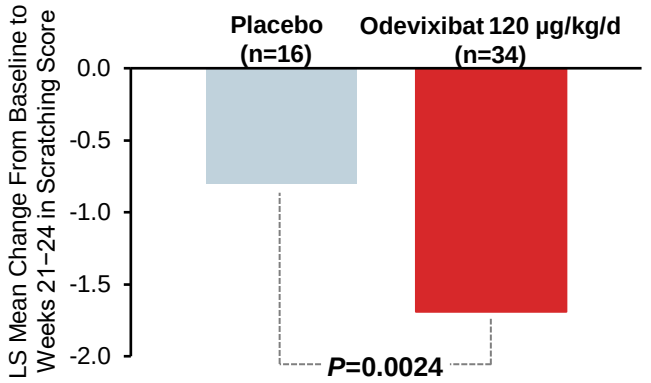
- Highly statistically significant reductions in pruritus and bile acid levels and improvements in sleep with odevixibat
- Early, rapid, and sustained improvements in pruritus, bile acids, and sleep
- Odevixibat was generally well tolerated; no patients discontinued the study

Conclusions

- In children with Alagille syndrome, treatment with odevixibat for 24 weeks led to significant improvements in pruritus severity, reductions in bile acids, and improvements in sleep relative to placebo

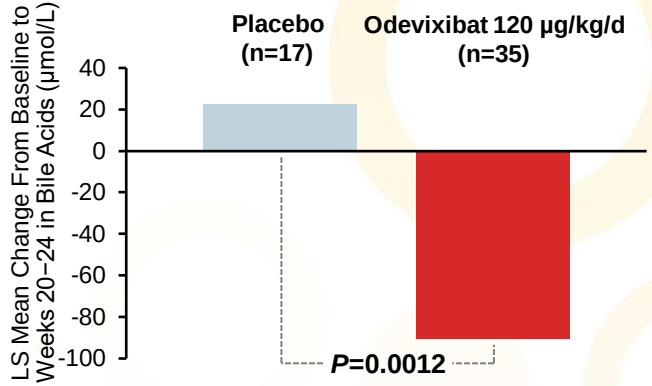
Scratching

Primary Endpoint



Bile Acids

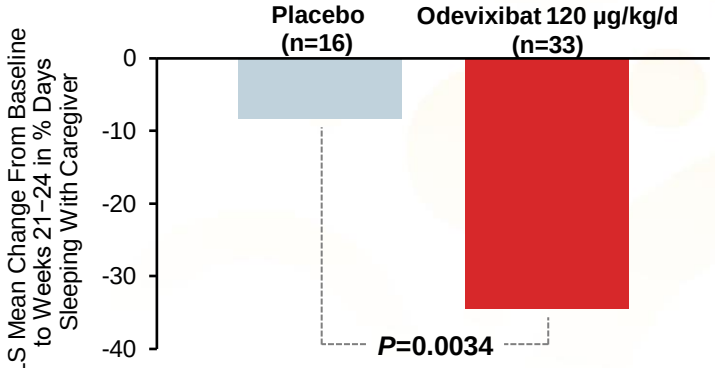
Key Secondary Endpoint



Sleep Parameters

Secondary Endpoint

Representative sleep parameter is shown; a total of 7 sleep parameters were evaluated



IBAT, ileal bile acid transporter; LS, least squares.

Ovchinsky N, et al., Abstract 38786.

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Pediatric Liver Disease

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