AASLD Nov. 12-15, 2021

The Liver Meeting®

DIGITAL **EXPERIENCE**

The Best of The Liver Meeting®

CHOLESTATIC AND AUTOIMMUNE LIVER DISEASES

About the program:

Best of The Liver Meeting 2021 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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Treatment with a JAK1/2 inhibitor alleviates autoimmune cholangitis in ARE Del mice

Hypothesis/Aim/Objective

- Modulation of type I/II IFN signaling pathway by a JAK inhibitor can be an effective therapeutic approach for PBC

Methods

- Determination of immunological and histopathological responses in Ruxolitinib treated female ARE-Del$^{+/-}$ mice model of PBC.

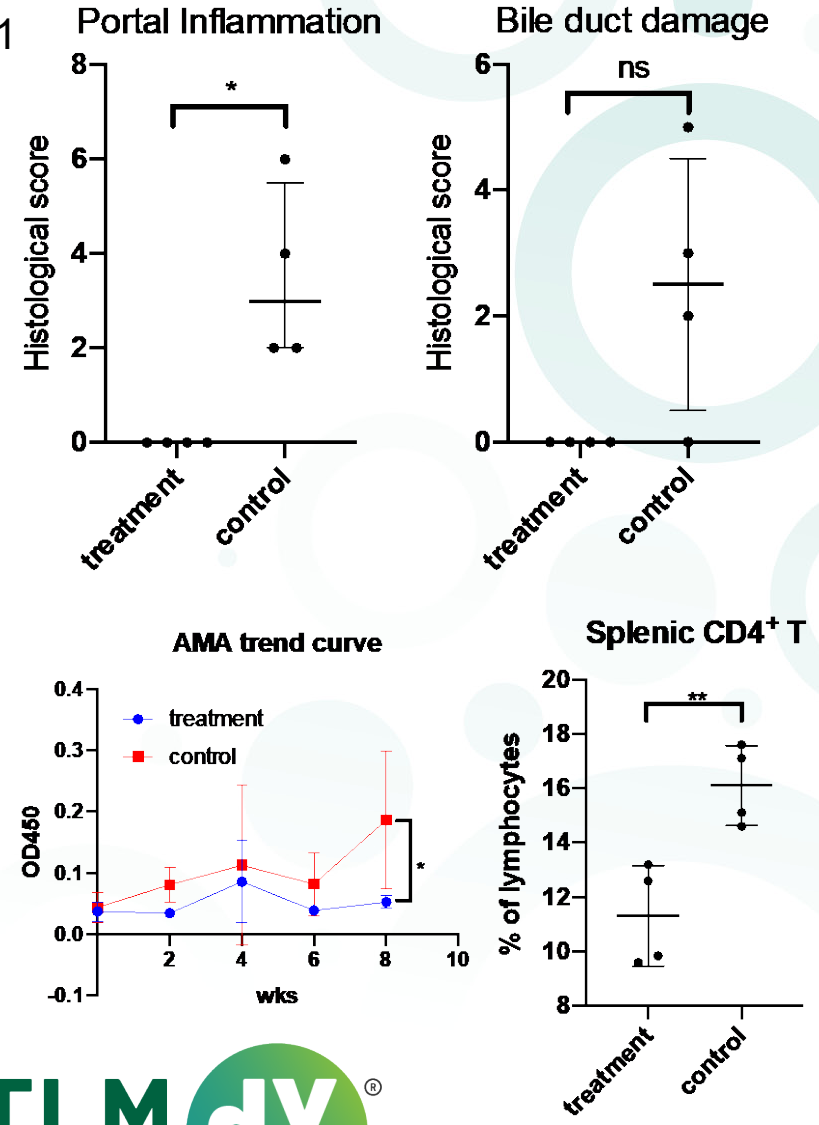
Main Findings

- Compared with control mice, portal inflammation and bile duct damage were highly reduced in Ruxolitinib administered mice, accompanied by a significant reduction in splenic CD4^{+} T cells and lower AMA levels (Fig.1).

Conclusions

- Ruxolitinib alleviates biliary pathology via suppression of CD4^{+}T cells in female ARE-Del$^{+/-}$ mice.

Fig.1



Shao T, et al., Abstract 121.

Dysregulated sphingolipid metabolism is associated with brain dysfunction in Mdr2 knock out mice

Hypothesis/Aim/Objective

The cholestatic liver injury-induced dysregulation of sphingolipid metabolism contributes to neurological disorders

Methods

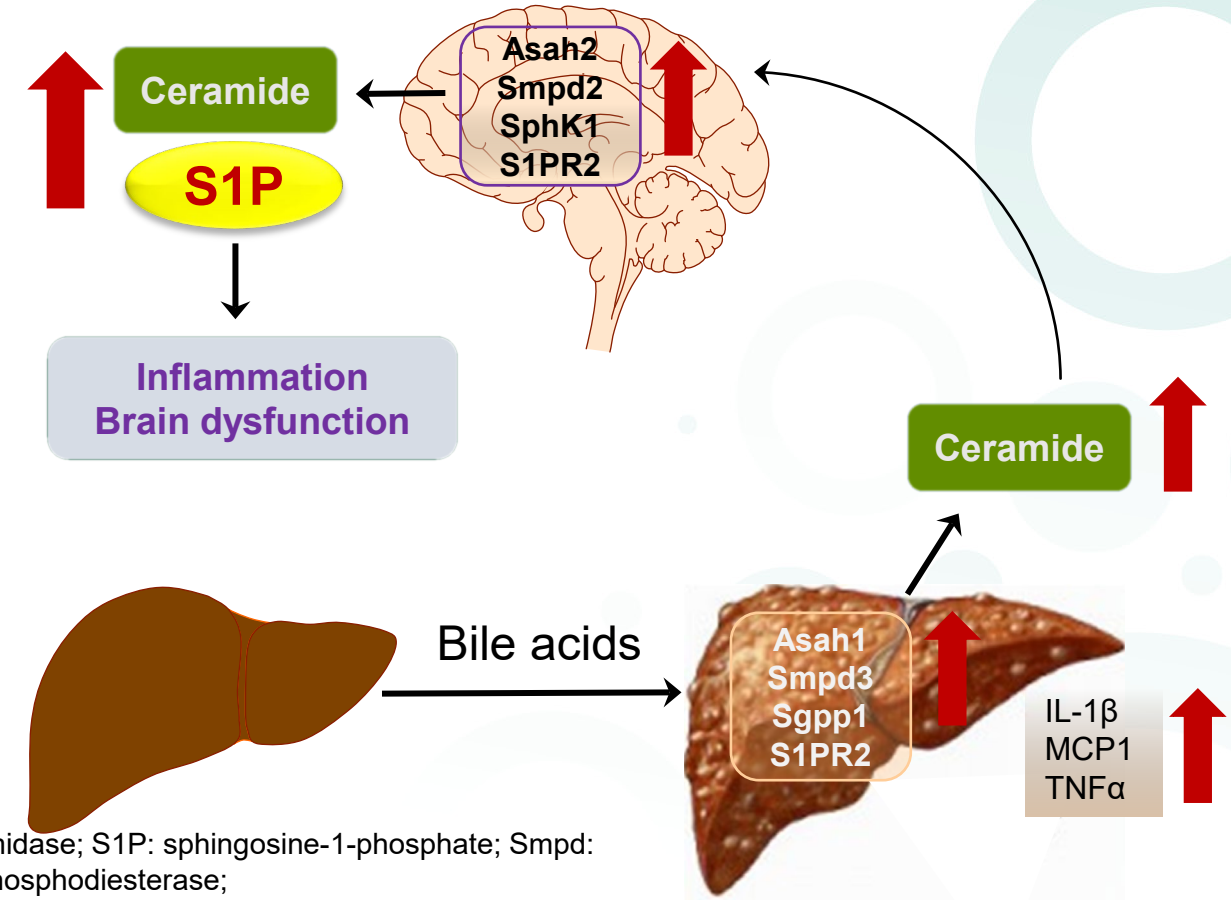
Age and gender matched wild type and Mdr2$^{-/-}$ mice were used to examine impact of cholestatic liver injury on brain function and sphingolipid metabolism.

Main Findings

The severity of cholestatic liver injury of the Mdr2$^{-/-}$ mice was associated with infiltration of CD11b^{+} myeloid cells in both the liver and brain. The mRNA levels of key inflammatory mediators, such as IL-1β and MCP-1, were significantly increased in the liver and brain. The key genes involved in sphingolipid metabolism were markedly upregulated, especially SphK1, Smpd2, and Asah2 in the brain and Asah1, Sgpp1, and Smpd3 in the liver. S1PR2 expression level was significantly increased in both the liver and brain.

Conclusions

Cholestatic liver injury-induced loss of sphingomyelin and the imbalance of sphingosine-1 phosphate and ceramide contributes brain dysfunction, especially memory loss.



Asah: Acid ceramidase; S1P: sphingosine-1-phosphate; Smpd: sphingomyelin phosphodiesterase;
sgpp1: S1P phosphatase 1; SphK1: sphinosine kinase 1; S1PR2: S1P receptor 2.

Zhao D, et al., Abstract 125.

TLM dX®

Patients with primary biliary cholangitis treated with long-term obeticholic acid in a trial setting demonstrate better transplant-free survival than external controls from the GLOBAL PBC and UK-PBC study groups

Objective

- Evaluate effect of obeticholic acid (OCA) on time to first occurrence of liver transplant or death in patients with primary biliary cholangitis (PBC)

Methods

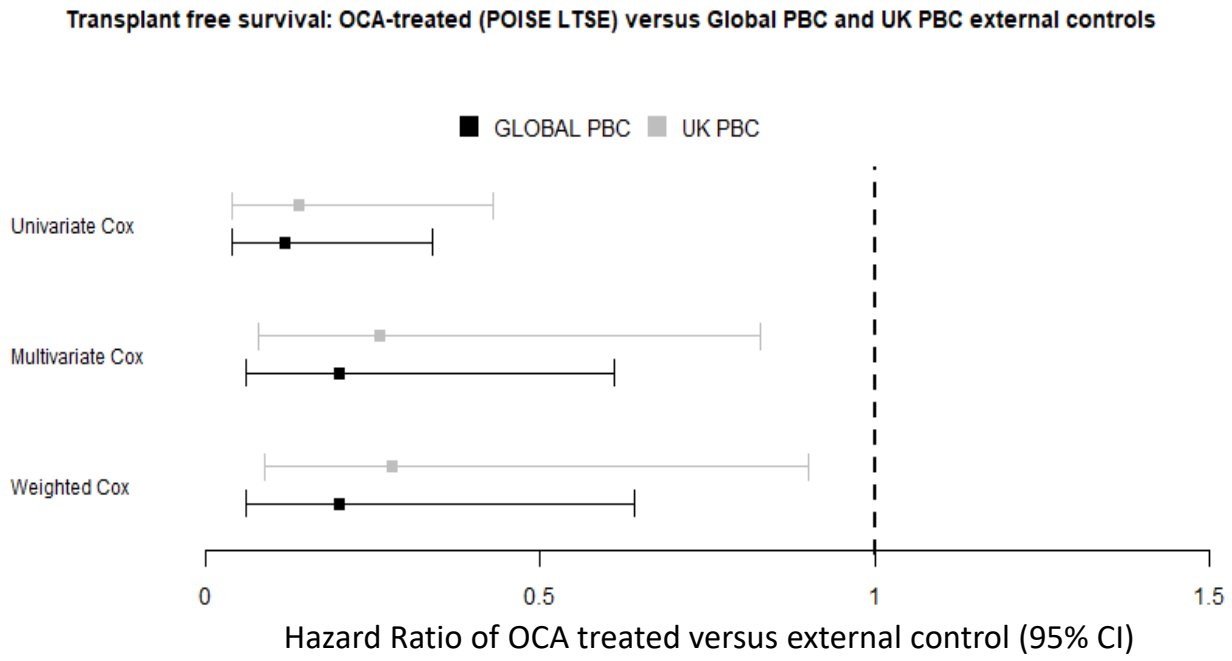
- Cox regression comparing time to composite endpoint of liver transplant or death in PBC patients treated with OCA in the POISE long-term safety extension trial vs. non-OCA-treated external controls from the GLOBAL PBC and UK-PBC registries, matched by trial eligibility criteria and using propensity scores.

Main Findings

- OCA-treated patients from the POISE study had statistically significant lower risk of liver transplantation/death compared to either external control group.

Conclusions

- These are the first data showing improvement in the occurrence of clinically important outcomes with obeticholic acid in patients with PBC.



Murillo Perez CF, et al., Abstract L08.

TLMdX®

Serum autoantibodies against annexin A11 may weaken the biliary bicarbonate umbrella in IgG4-related cholangitis (IRC)

Objective / Aim We recently identified annexin A11 as an IgG4-/IgG1-specific autoantigen in IgG4-related cholangitis (IRC). Here we studied a potential pathogenetic role of annexin A11 in IRC, focusing on elements of the protective 'biliary bicarbonate umbrella' machinery in the apical cholangiocyte membrane.

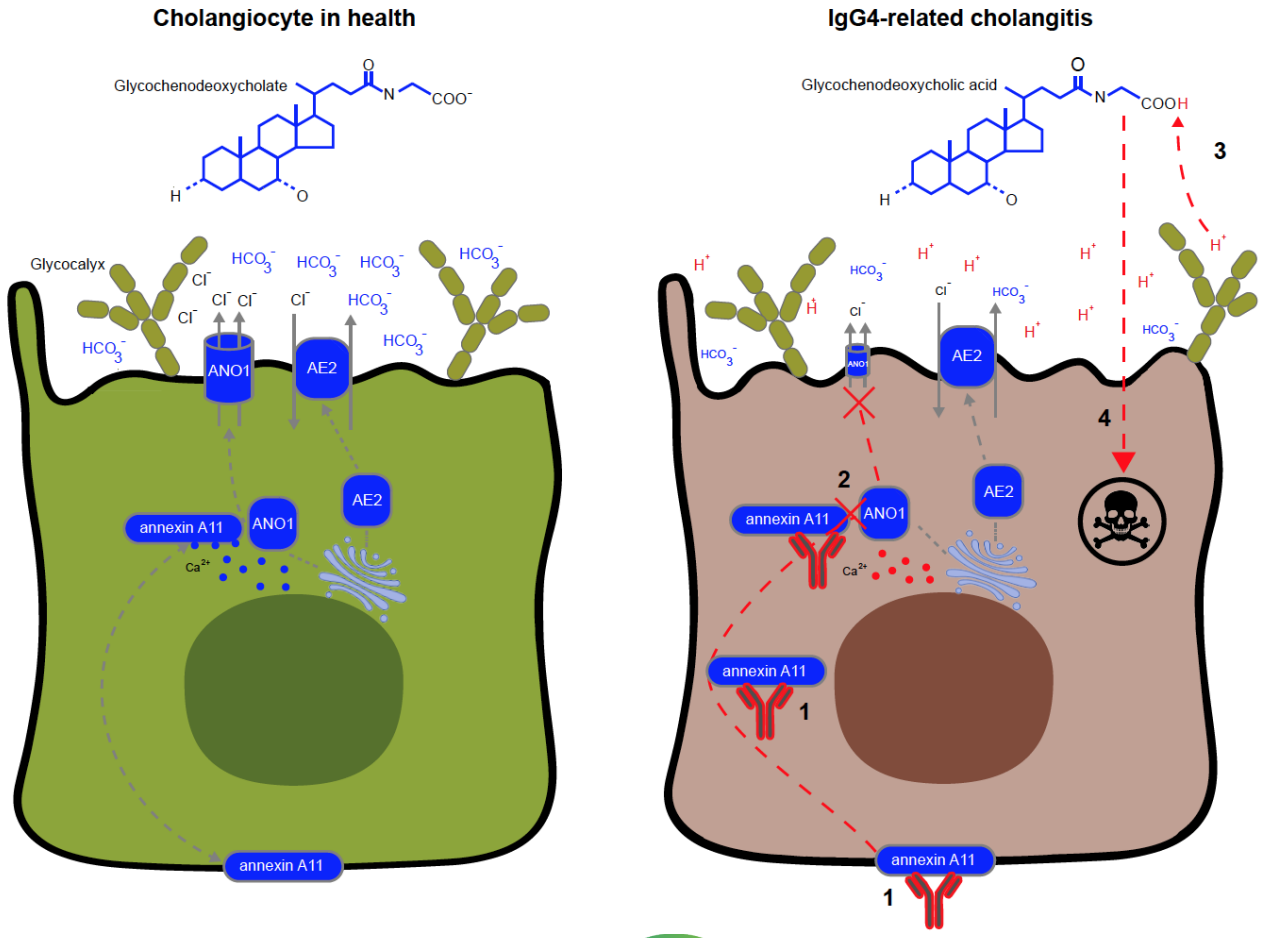
Methods

1. Human sham and *ANXA11* knockdown H69 cholangiocytes were subjected to intracellular pH measurements, cell surface biotinylations of key members of the biliary bicarbonate machinery, and radioactive bile acid permeation assays.
2. Annexin A11-eMerald and ANO1mCherry localization were assessed by live cell microscopy after incubation with IRC patient serum containing anti-annexin A11 IgG1/IgG4-autoantibodies and primary sclerosing cholangitis patient control serum.

Main Findings

1. *ANXA11* knockdown led to (i) reduced plasma membrane expression of the Ca^{2+}-sensitive chloride channel ANO1, but not the chloride/bicarbonate exchanger AE2, (ii) intracellular alkalinization, and (iii) uncontrolled bile acid influx.
2. High $[Ca^{2+}]_i$ conditions led to annexin A11 membrane shift and colocalization with ANO1. Incubation with IRC patient serum containing anti-annexin A11 IgG1/IgG4 autoantibodies inhibited annexin A11 membrane shift and reduced ANO1 surface expression.

Conclusions Anti-annexin A11 autoantibodies may contribute to the pathogenesis of IgG4-related cholangitis by weakening the 'biliary bicarbonate umbrella'.



Kersten R, et al., L09.

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