AASLD The Liver Meeting® Nov. 15-19, 2024

Experimental sclerosing cholangitis: effects of an anti-fibrotic strategy on the ductular reaction

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BACKGROUND

Primary sclerosing cholangitis (PSC) is an immune-mediated fibrotic and cholestatic liver disease that frequently progresses, ultimately leading to advanced hepatobiliary fibrosis, cirrhosis and end-stage liver disease and cancer risk. There are currently no evidence-based pharmacological treatments for PSC that is further marred by its frequent recurrence after transplantation.

Histopathologically, PSC is characterised by fibrosis that begins in the bile ducts but progresses to the portal tracts with portal-portal bridging and finally cirrhosis. The magnitude of fibrosis correlates closely with the extent of the 'ductular reaction' in which cells expressing biliary markers proliferate, forming small ductules.

DUCTULAR REACTION: THE DEBATE

While the ductular reaction is a well-recognized histopathological feature of a range of chronic liver diseases including the cholangiopathies, its significance is a matter of conjecture. Though the conventional point of view, based largely on correlative findings, suggests that the ductular reaction is detrimental (1), an alternate opinion indicates that it may be a beneficial response to injury (2).

1. Sato K, Pham L, Glaser S et al. Pathophysiological Roles of Ductular Reaction in Liver Inflammation and Hepatic Fibrogenesis. Cell Mol Gastroenterol Hepatol; 2023;15(3):803-805.
2. Monga SP, Nejak-Bowen K. Ductular Reaction and Liver Regeneration: Fulfilling the Prophecy of Prometheus! Cell Mol Gastroenterol Hepatol; 2023;15(3):806-808.

AIMS

With fibrosis as the key pathological feature of PSC that closely correlates with the extent of clinical disease, we postulated that inhibition of the prototypic profibrotic growth factor, transforming growth factor-ß, would:
1. ameliorate the structural & functional manifestations of disease in the DDC model of PSC
2. by examining its effects on the ductular reaction may also provide insight into whether this might be pathological or beneficial.

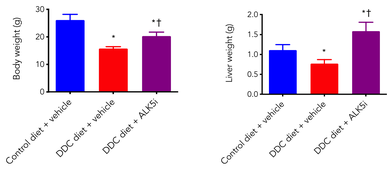
DDC MODEL OF CHOLANGIOPATHY

While no animal model of human disease is perfect, the DDC model closely recapitulates many of the biochemical and histopathological features of human PSC. In brief, 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) is a strong inducer of δ-amino-levulinic acid synthase that stimulates the synthesis and secretion of hepatotoxic protoporphyrins with formation of protoporhyrin plugs that obstruct small bile ducts. The resultant cholestasis is characterised by biliary fibrosis, cholestasis, biliary inflammation (cholangitis), portal tract fibrosis and ductular reaction akin to human PSC.

METHODS

We randomized mice to one of three groups:
a. regular diet (Taklad 2918), receiving vehicle via BID gavaging
b. regular diet mixed with 0.1% DDC diet, receiving vehicle via BID gavaging
c. regular diet mixed with 0.1% DDC diet, treated with the transforming growth factor-ß receptor type 1 kinase (ALK5) inhibitor, SB525334 (30 mg/kg bid)

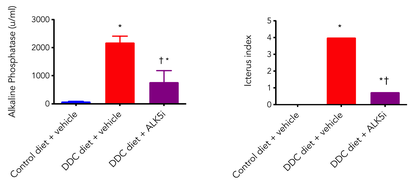
RESULTS: ANIMAL CHARACTERISTICS



Mice that received DDC had lower body weight that was ameliorated by ALK5 inhibition.
Liver weight was similarly reduced in DDC fed mice that was not only prevented by ALK5 inhibition but led to a significant increase in it.

* p <0.01 versus control diet, † p <0.01 versus DDC diet + vehicle

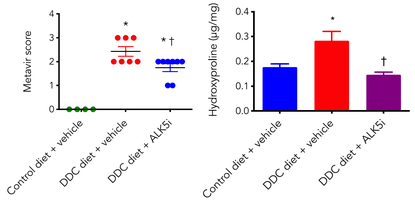
RESULTS: BIOCHEMISTRY



DDC-feeding of mice led to marked elevations in ALP and serum icterus index that were both substantially attenuated by ALK5 inhibition.

* p <0.01 versus control diet, † p <0.01 versus DDC diet + vehicle

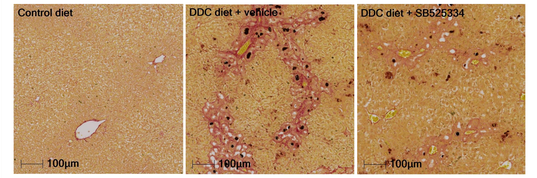
RESULTS: FIBROSIS



Hepatic fibrosis as measured by PSR staining (far left) using Metavir scoring was increased in DDC-fed mice and ameliorated by ALK5 inhibition as was liver hydroxyproline content (immediate left).

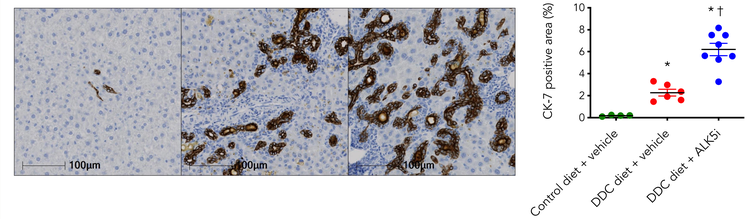
* p <0.01 versus control diet, † p <0.01 versus DDC diet + vehicle

RESULTS: FIBROSIS HISTOPATHOLOGY



Representative examples of picrosirius red stained liver sections showing marked fibrosis in DDC-fed mice that was ameliorated by ALK5 inhibition.

RESULTS: DUCTULAR REACTION



Bile duct cholangiocytes as assessed by +ve CK-7 immunolabelling were increased in DDC-fed mice and further increased in mice that had received the ALK5 inhibitor.

CONCLUSION

- DDC model recapitulates many of the features of PSC in humans including periductal fibrosis, increased collagen content, cholestatic biochemistry and ductal reaction.
- Interruption of the TGF-ß pathway using an inhibitor of its type 1 receptor led to:
  - ↓ histological fibrosis
  - ↓ liver collagen content
  - ↓ alkaline phosphatase
  - ↓ icterus index
  - ↑ liver mass
  - ↑ ductal reaction
- We speculate that hepatomegaly and ↑ ductal reaction are components of a beneficial (healing) response to injury rather than being part of the pathological process.