A novel CCL24 blocking monoclonal antibody ameliorates liver injury in experimental models of cholestasis

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EASL The Home of Hepatology
THE INTERNATIONAL LIVER CONGRESS™ 2018
APRIL 11-15, PARIS, FRANCE

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INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by progressive destruction of bile ducts caused by diffuse inflammation and fibrosis. Chemokines are proteins that share the ability to induce migration and activation of specific subsets of cells and play a critical role in inducing liver inflammation and fibrosis. CCL24, a pro inflammatory and profibrotic chemokine, was recently found to play a key role in the progression of inflammatory and fibrotic pathways. ChemomAb is developing CM-101, a novel CCL24 blocking monoclonal antibodyas treatment for fibrotic and inflammatory liver diseases with NASH as the primary indication. CM-101 was evaluated in animal models of PSC.

AIM

Expression of CCL24 and its receptor-CCR3 in PSC liver biopsies and mononuclear cell of PSC patients were evaluated.

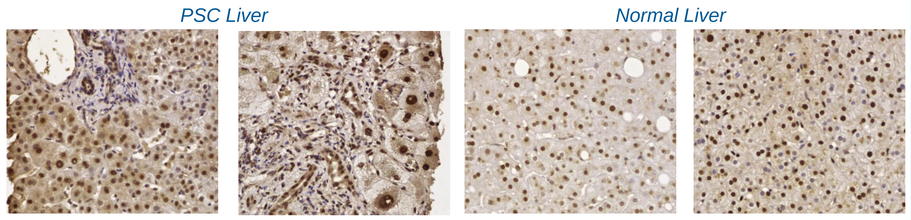
The novel CCL24 blocking monoclonal antibody, CM-101 was tested using two experimental animal models of cholestasis recapitulating features of PSC.

METHOD

- Immunohistochemistry was performed to detect CCL24 in liver biopsies from PSC patients.
- CCR3 expression on mononuclear cells were compared, using FACS, between PSC patients and healthy volunteers.
- The anti-fibrotic and anti-inflammatory effects of CM101 were evaluated in two animal models: bile duct ligation (BDL) in rats and acute α-naphthylisothiocyanate (ANIT) induced cholestasis in mice.
  - In the BDL model: Sprague Dawley rats (n=10 per group) underwent bile duct ligation. Two weeks following the ligation animals were treated with CM-101, 10mg/kg IV twice weekly for two weeks or matching vehicle.
  - In the acute ANIT induced cholestasis model: mice (n=8 per group) were treated with 60 mg/kg ANIT with or without a single IV dose of 10mg/kg CM101 and were scarified on day 3.

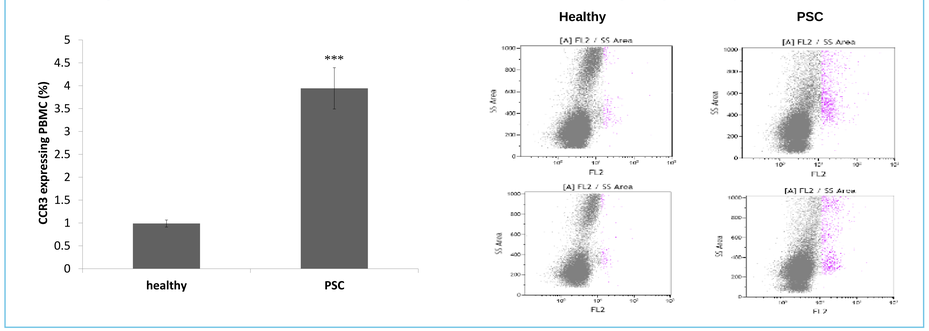
Overexpression of CCL24 in immune cells and Cholangiocytes

Immunohistochemistry staining of representative liver samples from PSC patients and healthy subjects.



CCR3 (CCL24-receptor) expression was increased in PBMC of PSC patient's

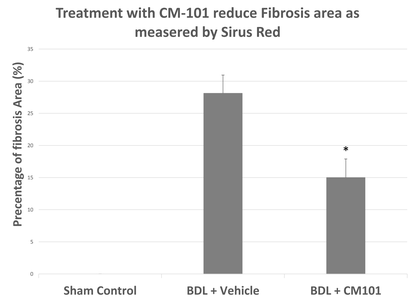
*FACS analysis of isolated mononuclear cells from PSC patients and healthy subjects. ***pv<0.001*

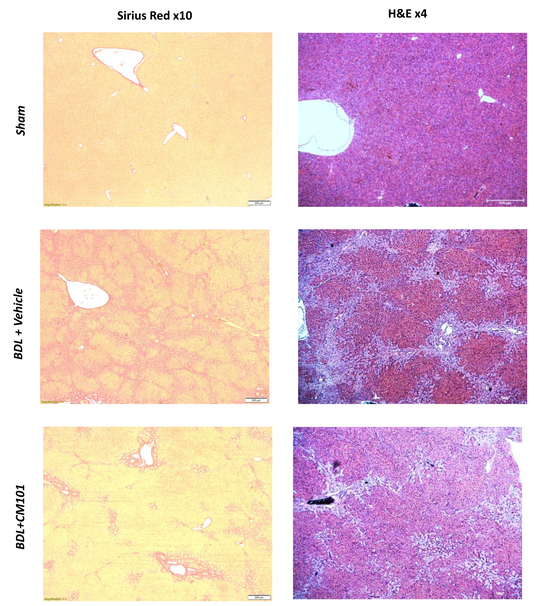


Bile duct ligation (BDL) rats model

Hepatic fibrosis was reduced in CM-101 treated animals compared to vehicle treated group.

Two weeks after bile duct ligation rats (n=10 per group) were treated with 10mg/kg CM-101 or vehicle for additional 2 weeks. CM-101 resulted in 50% reduction in the fibrosis area compared with the control treated group, p < 0.05

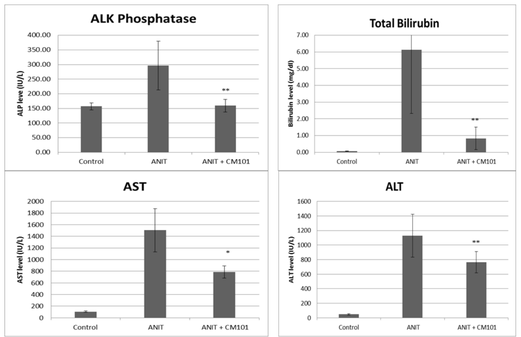




ANIT (α-naphthylisothiocyanate) induced cholestasis mice model

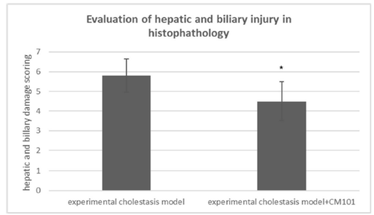
Liver enzymes were significantly reduced in CM-101 treated group (ANIT+CM-101) compared to vehicle treated group (ANIT).

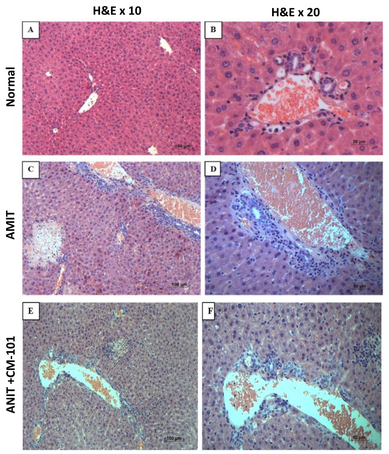
*Mice treated with ANIT on day 0 demonstrated significant elevation in Alkaline phosphatase, bilirubin, AST and ALT compared to control healthy mice. Mice treated with 5mg/kg CM-101 simultaneously to ANIT administration on day 0 exhibited significantly reduced liver enzymes compared to ANIT treated group. **pv≤0.01, *pv≤0.05*



Histological evaluation of hepatic and biliary injury in the ANIT model was reduced in CM-101 treated animals compared to vehicle treated group.

*Biliary necrosis, biliary neutrophilic infiltration, fibroblast proliferation and hepatic necrosis were scored 1-3 according to histological findings. CM101 treated animals demonstrated reduced scoring (4.5±1, n=8) compare to vehicle treated group (5.8±0.8, n=8) in ANIT induced cholestasis experimental model. Results are demonstrated as average ± SE .*pv≤0.05*





CONCLUSIONS

The CCL24-CCR3 axis is increasingly expressed in samples from patients with PSC compared to healthy subjects.

In-vivo blockage of CCL24 with the novel monoclonal antibody CM-101 resulted in attenuation of cholestasis and fibrosis in the ANIT and BDL experimental PSC models.

CCL24 therefore appears as an attractive new target for the treatment of PSC. ChemomAb is planning human clinical testing of CM-101 in PSC patients.

CONTACT INFORMATION

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