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

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 antibodies 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 N-phthalylisothiocyanate (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.

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.

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