CM-101 a Novel anti-CCL24 monoclonal antibody reduces cholangiocytes proliferation in experimental cholestatic models

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by progressive destruction of bile ducts, diffuse inflammation and fibrosis. Abnormal biliary hyperplasia and cholangiocyte proliferation are two main features of PSC. In previous studies ChemomAb showed robust expression of the chemokine CCL24 on cholangiocytes using liver biopsy samples taken from PSC patients. Furthermore, we were able to show that CM-101, a CCL24 blocking monoclonal antibody (mAb), reduced liver injury in a rodent bile duct ligation model of cholestasis, significantly attenuating liver fibrosis. In this study we aimed to characterize the relevance of CCL24 in the process of cholangiocyte proliferation and to test the ability of CM-101 treatment to reduce biliary hyperplasia and bile duct proliferation using two different cholestatic animal models.

AIM

To evaluate the effect of CM-101 (a first in class, novel CCL24 blocking monoclonal antibody) on biliary hyperplasia and bile duct proliferation in rodent models of cholestasis.

METHOD

The therapeutic effect of CM-101, a CCL24 novel blocking mAb, was evaluated in two rodent cholestatic experimental models:

- Chronic α-naphthylisothiocyanate (ANIT) induced cholestasis in mice
- The bile duct ligation (BDL) model in rats

In the chronic ANIT model mice were fed with ANIT diet (0.05%) for 4 weeks and treated with 5mg/kg of CM-101 or vehicle for the following 2 weeks. In the BDL model, rats were treated with either 10mg/kg CM-101 or vehicle for two weeks following the bile duct ligation. Liver damage, cholangiocyte proliferation and hyperplasia were characterized by Histopathological examination of H&E stained sections together with PAN-CK and K67 immunohistochemical staining.

RESULTS

CM-101 significantly reduced bile duct expansion and attenuated BDL induced liver damage

Bile duct ligation induced massive ductal proliferation and severe liver damage. Staining liver sections with H&E and PAN-CK, a specific marker of cholangiocytes, revealed significant attenuation of liver damage and a 50% reduction in PAN-CK staining in animals treated with CM-101.

CM-101 treatment in the BDL rat model resulted in decreased cell proliferation

Cell proliferation quantified by Ki67 staining, of bile duct ligated rats liver sections, showed a significant reduction of proliferation in the CM-101 treated group.

CM-101 reduced biliary hyperplasia in the ANIT Diet induced cholestasis mouse model

A 4 weeks ANIT diet induced peri-duetal liver damage and biliary hyperplasia.

Histopathological scoring of biliary hyperplasia (1-3) and PAN-CK cholangiocyte staining of liver sections from ANIT fed mice were used to evaluate liver injury. CM-101 treatment resulted in a significant 30% reduction in biliary hyperplasia and reduced ductal proliferation.

CONCLUSIONS

These findings further validate the relevance of CCL24 in cholestatic disease progression and liver damage. CM-101 treatment leading to CCL24 blockage, resulted in significant reduction of cholangioocyte proliferation and bile duct hyperplasia. This pre-clinical data from these experimental cholestatic models, suggests a potential therapeutic effect for CM-101 in PSC. CM-101 is therefore planned to be tested in a Phase 2 clinical trial in PSC patients.

REFERENCES


CONTACT INFORMATION

adimor@chemomab.com