CM-101, A novel CCL24 blocking antibody, suppresses hepatic injury and fibrosis in experimental models of NASH and liver fibrosis

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INTRODUCTION

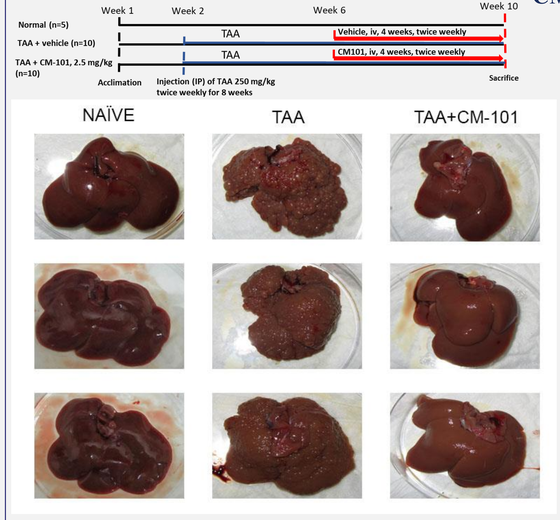
The chemokine system is known to play a key role in the development of hepatic inflammation and fibrosis (1). CCL24 is a pro-inflammatory and pro-fibrotic chemokine that was recently found to be overexpressed in the livers of Nonalcoholic steatohepatitis (NASH) and Primary sclerosing cholangitis (PSC) patients and to play a crucial role in liver damage. CM-101 is a first in class humanized IgG1 monoclonal antibody targeting human CCL24 that is currently in clinical development for the treatment of NASH and PSC. Here, we present the therapeutic effect of CM-101 on liver damage in two well established preclinical liver injury models of NASH and liver fibrosis (2).

METHODS

We evaluated the in vivo antifibrotic effect of CM-101 in rats with established fibrosis due to thioacetamide (TAA)-induced injury. Fibrosis was induced in female Wistar rats (n=10 per group) by intraperitoneal administration of TAA (150 mg/kg, for 8 weeks). CM-101 or vehicle control were administered concurrently with the TAA from week 5. Biochemical liver function, fibrotic and inflammatory markers and histologic evaluations of the liver were conducted.

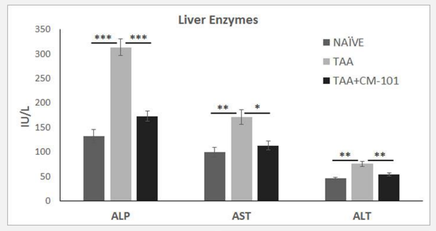
To evaluate CM-101 effect in NASH, the STAM™ murine model was used. Mice were injected once with Streptozotocin and fed with high-fat diet from week 4 for 9 weeks (n=8 per group). CM-101 or vehicle control were administered twice weekly from week 6. Histopathological analysis and quantification of collagen deposition were done by liver H&E and Sirius red staining.

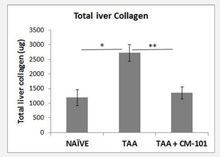
RESULTS

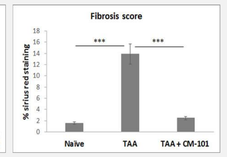


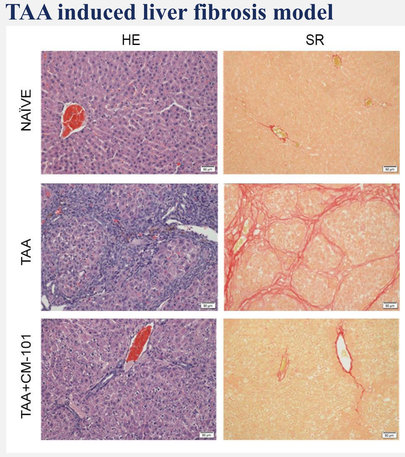
***pv<0.001, ** pv<0.005, *pv<0.01

CM-101 treatment robustly inhibits fibrosis in TAA induced liver fibrosis model

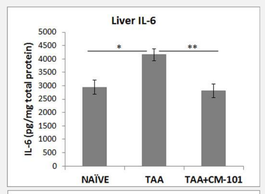


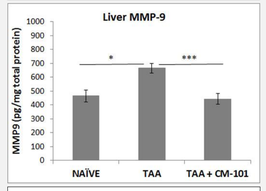






Macroscopic evaluation of CM-101 treated livers showed pronounced amelioration of liver pathology with significant reduction of regenerative nodules accompanied by decreased liver enzymes. Quantification of collagen levels by Sirius red staining demonstrated 80% reduction of liver fibrosis in the CM-101 treated livers.



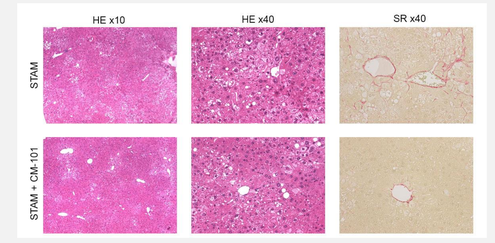


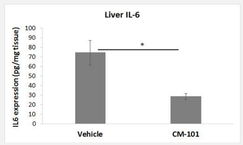
Liver IL-6 and MMP9 levels were elevated following TAA treatment.

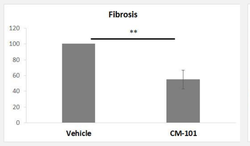
CM-101 reduced IL-6 and MMP-9 back to baseline levels.

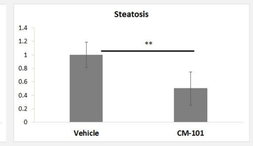
CM-101 attenuates Inflammation and Fibrosis in NASH STAM model

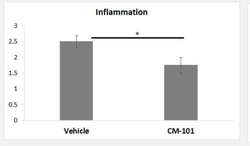
Histological scoring revealed that CM-101 treatment led to significant inhibition of NAFLD activity score and fibrosis. The improvement was attributed to reduced liver inflammation and steatosis and accompanied by reduced liver IL-6 levels.

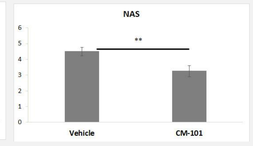












** pv<0.005, *pv<0.01

CONCLUSIONS

These findings further validate the role of CCL24 in liver fibrosis processes. Treatment with CM-101, a novel CCL24 blocking antibody, significantly attenuated liver damage and fibrosis in the TAA and STAM liver disease models. CM-101 is currently being tested as treatment for NAFLD/NASH and a study in PSC patients is underway.

REFERENCES

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2.Lefebvre E. Plos One, 2016 Jun 27;11(6)

CONTACT INFORMATION

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