Attenuating liver fibrosis and inflammation: blocking CCL24 inhibits recruitment of hepatic stellate cells, monocytes and neutrophils, and modulates hepatic stellate cell activation

Raanan Greenman 1, Ophir Hay 2, Inbal Mishalian 2, Ilan Vaknin 1, Massimo Pinzani 3,4, Douglas Thorburn 3,4, Johnny Amer 2, Ahmad Salhab 2, Rifaat Safadi 2, Adi Mor 1, Amnon Peled 2

1 Chemomab Therapeutics, Israel & United States
2 Hadassah Hebrew University Hospital, Israel
3 Royal Free London NHS Foundation Trust, United Kingdom
4 UCL Institute of Immunity & Transplantation, United Kingdom

INTRODUCTION

The chemokine system plays a pivotal role in hepatic inflammation and fibrosis development. CCL24, a pro-inflammatory and profibrotic chemokine, was found to be overexpressed in fibrotic liver conditions such as Primary sclerosing cholangitis (PSC) and Metabolic dysfunction associated steatohepatitis (MASH), contributing to liver damage. Numerous liver disease models have shown that blocking CCL24 attenuates disease progression. CM-101 is an IgG1 monoclonal antibody that neutralizes CCL24 activity and is currently undergoing clinical development for PSC treatment.

AIM

To investigate the mechanism by which CCL24 blockade ameliorates liver damage, focusing on its impact on cell trafficking and activation of key cell populations: liver macrophages and hepatic stellate cells (HSC).

METHODS

- Liver expression: biopsies were examined for CCL24 and CCR3 expression by immunohistochemistry and immunofluorescence.
- Activation of HSC: the fibrotic marker SMA (smooth muscle actin) was assessed by flow-cytometry in the human LX2 cell line, following 24-hour incubation with CCL24 with CM-101 or isotype control antibody.
- Immune cell recruitment: immune cell composition was examined following intra-peritoneal (i.p.) injection of CCL24 by scRNA-seq or by flow-cytometry.
- Animal models: the effect of CM-101 was tested in Mdr2-/- and ANIT-fed mice models of PSC. Liver samples were analyzed by immunohistochemistry and immunofluorescence to detect collagen deposition (Sirius Red stain), cholangiocytes (PanCK), macrophages (Iba1) and neutrophils (CXCR2 or Gr1).

RESULTS

CCL24 and its receptor, CCR3, are highly expressed in PSC and NASH livers

CCL24 recruits neutrophils and monocytes

CCL24 blockade reduces fibrosis and immune cell accumulation in preclinical models

CONCLUSIONS

- CCL24 induce motility and activation of HSC.
- CCL24 recruits neutrophils and monocytes to injured biliary areas.
- CM-101, a CCL24 neutralizing antibody, exhibits anti-inflammatory and anti-fibrotic effects.
- CM-101 interferes with the migration and activation of hepatic stellate cells, neutrophils and monocytes.
- Topline results from CM-101 phase 2a trial in PSC patients are expected in midyear 2024.

REFERENCES


CONTACT INFORMATION

Raanan.Greenman@Chemomab.com