CM-101, a Novel CCL24 Blocking Monoclonal Antibody, Attenuates HSC Activation and Reduces Fibrosis in the TAA Murine Model

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INTRODUCTION

CCL24 (C-C chemokine ligand 24, Eotaxin-2) is a chemokine that regulates inflammatory and fibrotic activities through its receptor, CCR3. This chemokine was found to be highly expressed in the livers of Nonalcoholic Steatohepatitis (NASH) and Primary Sclerosing Cholangitis (PSC) patients. Reduction of CCL24 was associated with decreased liver damage, most significantly by reducing fibrosis, in several experimental murine models. 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. The aim of this pre-clinical work was to study the role of the CCL24-CCR3 axis in liver fibrotic processes, both in vivo and in-vitro, and to evaluate the anti-fibrotic activity of CCL24 blockade using CM-101.

AIM

• To study the role of the CCL24 in liver fibrosis and hepatic stellate cell activation.
• Explore the anti-fibrotic activity of CCL24 blockade using CM-101.

MATERIAL & METHODS

Activation of hepatic stellate cells (HSC) by CCL24 was evaluated in the human LX2 cell line using the scratch motility assay, quantification of the fibrotic marker α-SMA and production of pro Collagen 1. Preincubation with CM-101 was used to block CCL24 induced activity of LX2 cells.

To evaluate the in-vivo effect of CM-101 on development of fibrosis we used the murine model of thioacetamide (TAA)-induced liver injury¹. Male BALB/C mice (6-8 weeks) received IP injections of TAA for 12 weeks twice weekly and either vehicle control (PBS), or CM-101 (D8) 2.5 mg/kg (CM-101 murine surrogate) concurrently by SC injections. Fibrosis was evaluated by histopathological analysis of H&E stained liver sections and quantification of collagen deposition in Sirius red stained slides. Gene expression of α-SMA, TIMP-1 and Col3a1 were tested against GAPDH normalization by Real-time PCR using TaqMan probes.

REFERENCES

1 Segal-Salto M et al. A Blocking Monoclonal Antibody to CCL24 Alleviates Liver Fibrosis and Inflammation in Experimental Models for Liver Damage (2019, Submitted)
2 Wallace MC et al. Standard operating procedures in experimental liver research: thioacetamide model in mice and rats (2015)

RESULTS

CM-101 significantly reduces α-SMA, TIMP-1, and Col3a1, that are associated with increased ECM formation, were all significantly upregulated in TAA mice. In accordance with histological analysis, CM-101 (DB) treatment significantly reduced the expression of these genes in the liver. (n=5)

CONCLUSION

CCL24 is a potent activator of HSC, affecting their motility and fibrogenic gene expression. CCL24 blockade using CM-101, a specific anti-CCL24 monoclonal antibody, reversed HSC activation in-vitro and reduced fibrosis development in-vivo in the TAA-murine model.

These findings further support the role of CCL24 as a therapeutic target in liver fibrotic diseases and the anti-fibrotic activity of CM-101.

Two phase Ia studies testing CM-101 in NASH and PSC are planned during 2020.

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CM-101 significantly reduces CCL24 induced LX2 cell activation

CCL24 induced LX2 cell activation increases α-SMA (alpha-smooth muscle actin) expression and secretion of Pro-Collagen 1. Pre-incubation of CCL24 with CM-101, markedly attenuates HSC activation, resulting in significant reduction of both α-SMA expression and Pro-Collagen 1 secretion. (A) FACS staining for α-SMA in LX2 cells; (B) evaluation of pro-collagen secretion by ELISA.