CCL24 BLOCKADE ATTENUATES BILIARY INFLAMMATION BY INTERFERING WITH MONOCYTE AND NEUTROPHIL RECRUITMENT

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Introduction

Primary Sclerosing Cholangitis (PSC) is characterized by the damaged peribiliary space, in which immune cells, reactive bile epithelial cells and fibroblasts from different sources interact, leading to elevation of cytokines, chemokines and a variety of other secreted factors that contribute to the inflammatory process. The chemokine CCL24 has been shown to help drive these self-reinforcing processes in fibrotic-inflammatory diseases, and its blockade was shown to ameliorate PSC progression in animal models.

Aim

We aim to study the role of CCL24, a chemokine that promotes immune cell trafficking and activation as well as pro-fibrotic activities at inflammatory sites in PSC pathophysiology.

Specifically, we examined the role of CCL24 and its blockade using CM-101, a CCL24 neutralizing antibody, on the trafficking of immune cells to tissues with a high presence of CCL24.

Methods

• Immune cell recruitment to CCL24-enriched areas was examined in diseased liver and following intraperitoneal (i.p.) injection of CCL24.
• We treated Mdr2-/- mice, a PSC model, with the neutralizing antibody CM-101. Immune cell composition was analyzed in blood and liver by FACS and immunohistochemistry.
• Peritoneal immune cell populations of intraperitoneally-injected animals were then analyzed by single-cell RNA sequencing (scRNA-seq) and by FACS.

CCL24 blockade using CM-101 inhibited accumulation of peribiliary macrophages and neutrophils.
• CCL24 i.p. injection induced recruitment of monocytes and neutrophils, in a manner distinctive to CCL24 (compared with CCL11 injection), and upregulated CCL24 expression in macrophages and dendritic cells.
• CM-101 pretreatment prevented recruitment of monocytes and neutrophils.

“SPRING” PSC Clinical Trial

CM-101 Phase 2 Trial in Primary Sclerosing Cholangitis Randomized, Double-Blind, Placebo-Controlled

Territories: US, UK, Germany, Spain, Israel
Key Enrollment Criteria:
• PSC patients with severe duct disease of >24 weeks duration
• ALP > 1.5 ULN
• Stable IBD allowed
• Stable UDCA treatment allowed
Outcome Measures:
• Primary - Safety
• Secondary - Change from baseline to Week 15 in:
  - Serum alkaline phosphatase
  - ELF score
  - Fibrotic biomarkers/liver enzymes-AST, ALT, Pro-C3, Pro-C5 & Fibroscan
  - Pharmacokinetics
  - Anti-Drug Antibody
  - Pharmacodynamic parameters
ClinicalTrials.gov Identifier: NCT04595825

Conclusions

• Monocytes and neutrophils are major players in PSC pathophysiology.
• Two in-vivo models for immune cell trafficking demonstrate clear CCL24-dependent recruitment of these immune cells. These inflammatory effects are unique to CCL24 compared with CCL11.
• CM-101, a first-in-class CCL24 neutralizing mAb, demonstrated an anti-inflammatory effect by interfering with migration of these cells to the damaged biliary area in a PSC model.
• CCL24 is a promising therapeutic target for PSC treatment. CM-101 is currently being tested in a Phase 2a study in PSC patients.

Disclosures

RG, IV, MSS, AK, OL and AM are employees of Chemomab
AP is a consultant to Chemomab

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