TREATMENT WITH THE CCR2/CCR5 ANTAGONIST CENICRIVIROC DOES NOT AFFECT MASH AND FIBROSIS DEVELOPMENT IN LDLR-/-.LEIDEN MICE, TRANSLATIONAL TO CLINICAL PHASE 3 TRIAL RESULTS

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Introduction

Cenicriviroc (CVC) is a dual CCR2/CCR5 antagonist that was in development for the treatment of metabolic dysfunction-associated steatohepatitis (MASH) and associated fibrosis.

While CVC showed antifibrotic potential in the phase 2B CENTAUR trial, the phase 3 AURORA trial was terminated after 1y due to lack of efficacy on improvement of fibrosis.

In contrast with these results in humans, many preclinical studies have shown anti-inflammatory and anti-fibrotic efficacy of CVC – which brings into question the translational value of these models for human MASH.

Aim

Study the effects of CVC treatment in the Ldlr-/-.Leiden mouse model for obesity-associated MASH and liver fibrosis, to investigate if this model can more accurately predict treatment effects in MASH patients

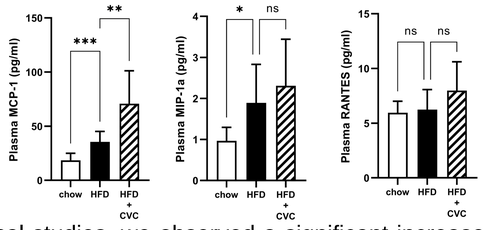
Methods

Male Ldlr-/-.Leiden mice were fed a MASH and fibrosis-inducing high-fat diet (HFD) for 20 weeks, after which the 14-week treatment with CVC (20 mg/kg BW, provided as dietary admix) was started in one group of mice (HFD+CVC) and another group of mice was kept on HFD as an untreated control. A chow-fed group was included as an aging reference. All mice were terminated at t=34 weeks for histological and biochemical analysis of MASH and fibrosis development as well as analysis of MASH- and fibrosis-related biomarkers.

CVC shows target engagement as observed in clinical trials

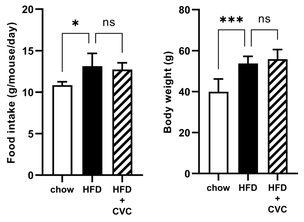
Clinical trials: increased plasma levels of CCR2 and CCR5 ligands.

- CCR2 ligand: CCL2 (MCP-1)
- CCR5 ligands: CCL3 (MIP-1α), CCL4 (MIP-1β) and CCL5 (RANTES)



In line with observations in clinical studies, we observed a significant increase in plasma MCP-1 and non-significant increases in MIP-1a and RANTES, indicative of adequate target engagement.

Effect of CVC on obesity and metabolic risk factors

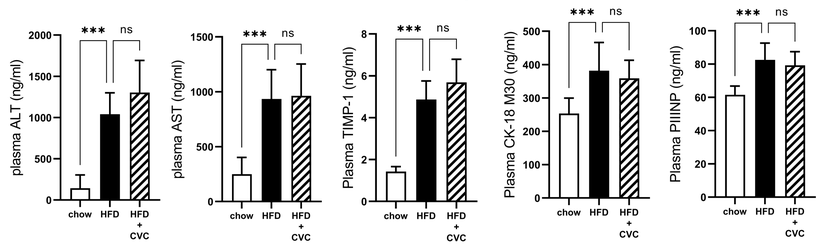


Effects of CVC treatment on metabolic risk factors in week 28

	chow	HFD	HFD +CVC
Blood glucose (mM)	6.9 ± 0.8[a]	7.9 ± 0.7[b]	7.2 ± 0.6[a]
Plasma insulin (ng/ml)	2.3 ± 2.0[a]	9.6 ± 5.7[b]	13.7 ± 6.4[b]
Plasma cholesterol (mM)	8.1 ± 2.1[a]	35.5 ± 6.2[b]	38.6 ± 8.9[b]
Plasma triglycerides (mM)	1.0 ± 0.6[a]	6.7 ± 1.9[b]	8.9 ± 3.0[c]

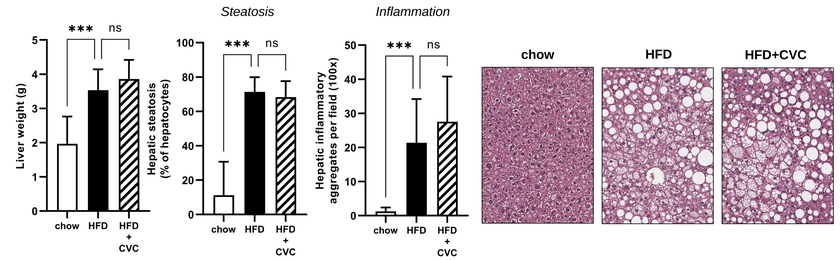
Treatment with CVC did not affect food intake and body weight. CVC lowered fasting blood glucose relative to HFD controls in week 28 of the study, but did not affect plasma insulin, plasma cholesterol or plasma triglycerides.

CVC does not affect ALT and AST or plasma markers of fibrosis

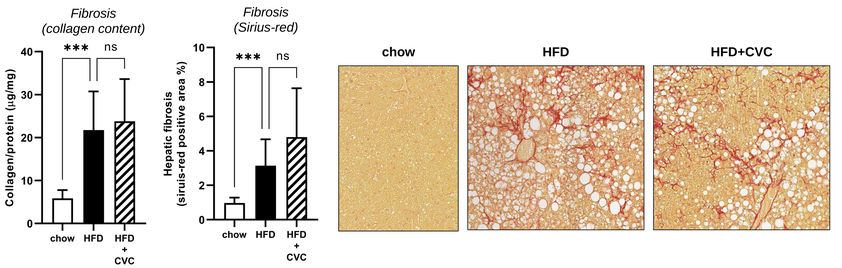


CVC did not affect plasma levels of the liver damage markers ALT and AST or the fibrosis markers TIMP-1, CK-18 M30 or PIIINP (measured in terminal plasma).

CVC does not affect liver steatosis, inflammation or fibrosis



Treatment with CVC did not affect liver weight. Analysis of HE-stained sections by a pathologist showed that CVC also had no effect on total steatosis or hepatic inflammation.



As observed in the phase 3 AURORA trial, treatment with CVC did not affect hepatic fibrosis, as demonstrated by biochemical analysis of collagen and by image analysis of Sirius-red-stained liver sections.

Conclusion

While many preclinical models have shown efficacy of CVC that contrasts clinical observations, CVC treatment (at a translational dose that did show efficacy in other preclinical models) in the HFD-fed Ldlr-/-.Leiden mouse did not reduce hepatic fibrosis – in line with the outcome of the phase 3 AURORA trial. This lack of effect was observed despite adequate target engagement, similar to clinical observations.

These findings underline the importance for validation of preclinical MASH models not only with treatments that have been found to have clinical efficacy, but also with treatments that have failed clinically.

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