Anti-inflammatory and anti-fibrotic effects of icosabutate as mono- or combination therapy with a GLP-1 receptor agonist, a FXR agonist or an ACC inhibitor in a dietary mouse model of progressive fibrosis

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Introduction

- Icosabutate (ICOSA), a semi-synthetic eicosapentaenoic acid derivative targeting FFA4 and the arachidonic acid cascade, is currently in P2b clinical development for the treatment of NASH (NCT04052516).
- To assess if additional anti-inflammatory and/or anti-fibrotic effects could be achieved via combination therapy, a comparison of ICOSA, firsocostat (FIR), a liver-targeted acetyl-coenzyme A carboxylase (ACC 1/2) inhibitor, semaglutide (SEMA, an injectable glucagon-like 1 (GLP-1) receptor agonist) or obeticholic acid (OCA, a farnesoid X receptor agonist) as monotherapies was performed in a choline-deficient, L-amino acid defined high-fat (46%) diet fed CDDA-HFD mouse model.
- The effects of combining ICOSA with either FIR, SEMA or OCA were simultaneously assessed, in addition to hepatic eicosanoid concentrations by LC-MS/MS in the ICOSA and SEMA groups only.

Methods

- Male C57BL/6JRj mice were fed CDDA-HFD (A16092001, Research Diets) for 6 weeks before treatment start. A baseline control group (n=12) was terminated at study start.
- CDDA-HFD fed mice (n=10-12 per group) received daily per oral (PO) treatment with vehicle (corn oil), ICOSA (112mg/kg), OCA (30mg/kg), SEMA (30nmol/kg SC), FIR (5mg/kg) as monotherapy or combinations of ICOSA + either SEMA, OCA or FIR (all dosing as for monotherapy) for 8 weeks Inflammation and fibrosis was assessed in terminal liver biopsy by IHC, biochemical and morphometric assays. Values expressed as mean ± SEM, n = 9-12 per group.

Results

Body weight. Equivalent body weight at randomisation (left) but SEMA treated mice have 26% lower bodyweight (p<0.001 vs. vehicle) at study end (right) as both mono- and combination therapy secondary to decreased food consumption (not shown).

Hepatic inflammation. As monotherapy, ICOSA reduced inflammatory foci by 47% (below left) and galectin-3 (a macrophage marker) by 26% (right). All combinations achieved significant reductions of both foci and galectin-3, the most pronounced effect achieved by ICOSA + SEMA (73% and 45% for inflammatory foci and galectin-3 respectively).

Hepatic fibrosis. ICOSA and SEMA significantly reduced hydroxyproline (HYP) content (by 33 and 22% respectively). ICOSA was also the only monotherapy that induced a significant anti-fibrotic effect as measured by picrosirius red (PSR)-morphometry (right). Optimal combination effects were observed in the ICOSA + SEMA group (-46% and -45% for PSR and HYP respectively).

Conclusions

- As monotherapy, ICOSA is a more potent anti-inflammatory/anti-fibrotic compound than either SEMA, OCA or FIR in a delayed treatment CDDA-HFD NASH mouse model.
- ICOSA significantly enhanced the anti-inflammatory and anti-fibrotic effects of SEMA and offered the optimal combination therapy.
- Mechanistically, ICOSA potently inhibits the hepatic arachidonic acid, a highly relevant target for the treatment of human NASH (1) and NASH driven fibrosis (2).