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Combination Treatment of a GPR119 Agonist DA-1241 with a DPP4 Inhibitor Synergistically Improves Systemic and Hepatic Inflammation in NASH Mice

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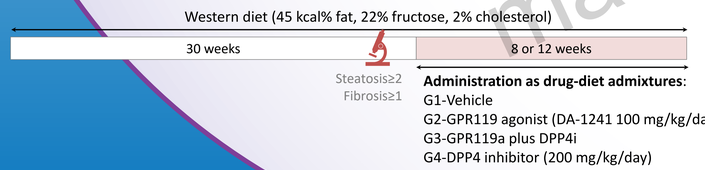
Background

- Chronic inflammation exacerbates liver damage and accelerates liver fibrosis
- DA-1241 is a G-protein coupled receptor 119 (GPR119) agonist under early clinical development for the treatment of type 2 diabetes in the USA.
- In addition to their own therapeutic effects on non-alcoholic steatohepatitis (NASH) independent of glucagon-like peptide-1 (GLP-1) action, GPR119 activation enhances GLP-1 secretion from intestinal L-cells, while DPP4 inhibition prolongs the biological half-life of plasma GLP-1.
- GLP-1 also has anti-NASH effects, which was verified clinically by liraglutide.
- So, their combination can maximize endogenous GLP-1 action. This study was intended to investigate the therapeutic potential of their combination for NASH.

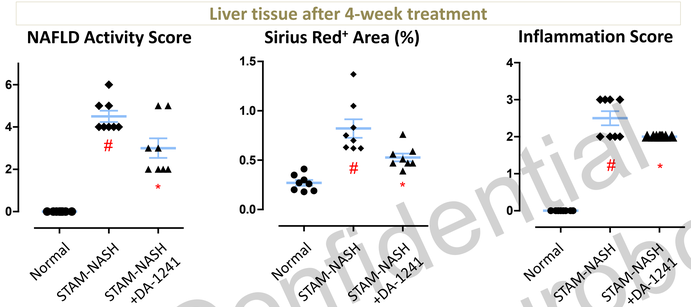
Methods

1. STAM-NASH Mice

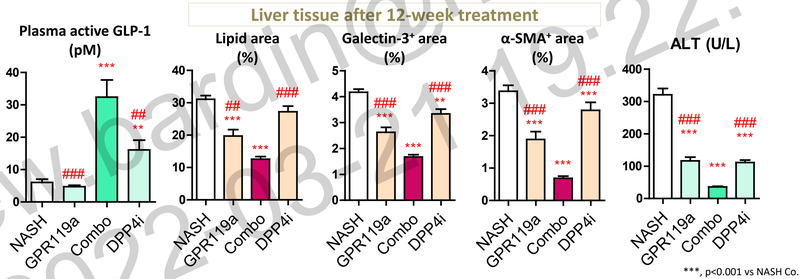
2. Diet-induced NASH Mice

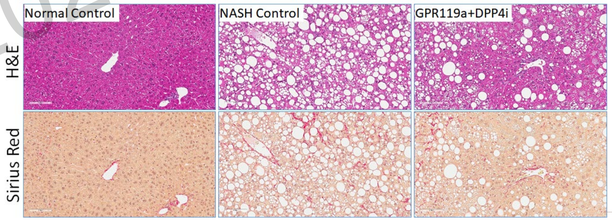


1. Anti-NASH effects in STAM-NASH mice

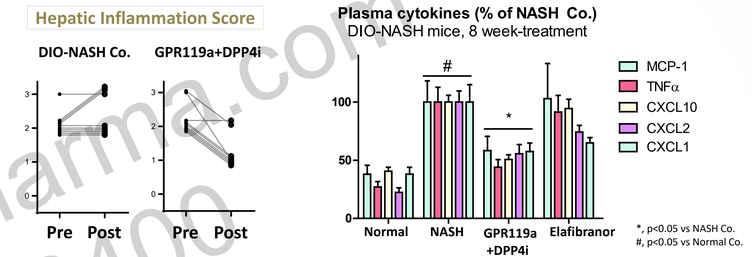


2. ANTI-NASH effects augmented by combination with DPP4 inhibitor in DIO-NASH mice

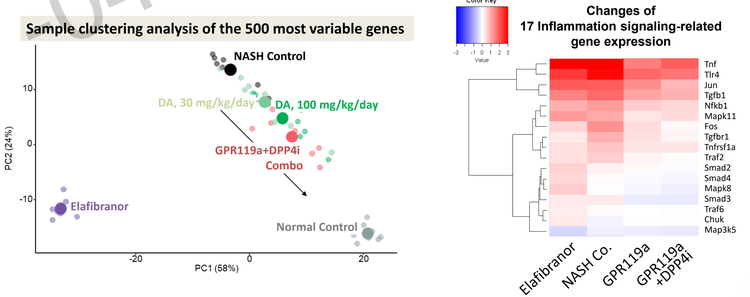




3. Improvement of hepatic and systemic inflammation



4. Restored transcriptome patterns of the liver in DIO-NASH mice



Conclusion

- This study firstly demonstrated synergistic benefits of GPR119 agonist with DPP4 inhibitor against NASH, particularly in local and systemic inflammation.
- We are planning to initiate POC study to explore clinical efficacy of DA-1241 in NAFLD patients and Phase 2 study in T2D patients next year.

Financial Disclosure

- None

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