DA-1241, a GPR119 agonist, combined with Semaglutide synergistically improved liver fibrosis in mice with CCl_4-induced liver fibrosis

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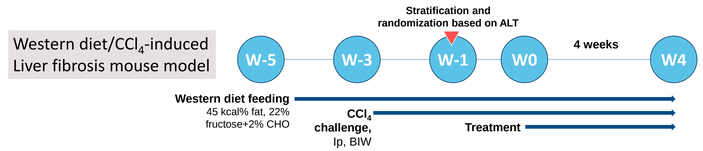
Introduction and Aim

DA-1241 is a novel chemical drug candidate that selectively and efficiently activates GPR119 and is currently in Phase 2a clinical development for the treatment of metabolic dysfunction-associated steatohepatitis (MASH). Previous study has confirmed that DA-1241, combined with dipeptidyl peptidase-4 (DPP4) inhibitors, synergistically enhanced the anti-MASH effect through increasing plasma active GLP-1 levels compared to each treatment alone. In connection with this, in this study, we attempted to determine the combination effects of DA-1241 and semaglutide (a GLP-1 analogue) on liver fibrogenesis.

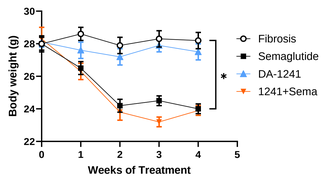
Method



Termination at 24 h post-dose of DA-1241 and 72 h post-dose of semaglutide

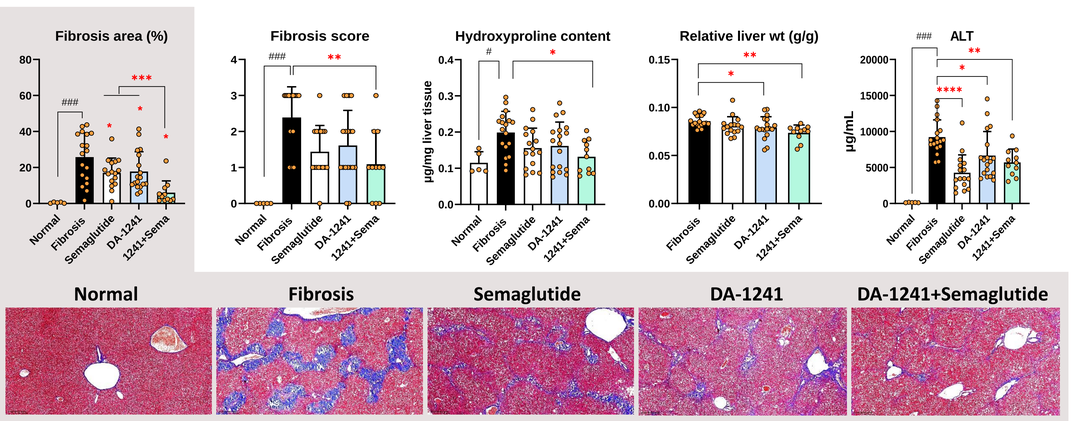
Group	Treatment	Dosing regimen
Normal Co.	Saline + 0.5% MC	Same schedule
Fibrosis Co.	Saline + 0.5% MC	Same schedule
Semaglutide (sc)	Semaglutide + 0.5% MC	250 nmol/kg, BIW + N/A, QD
DA-1241 (po)	Saline + DA-1241	N/A, BIW + 100 mg/kg, QD
DA-1241 (po) + Semaglutide (sc)	DA-1241 + Semaglutide	100 mg/kg, QD + 250 nmol/kg, BIW

No additional body weight loss was observed by adding DA-1241 on top of semaglutide.

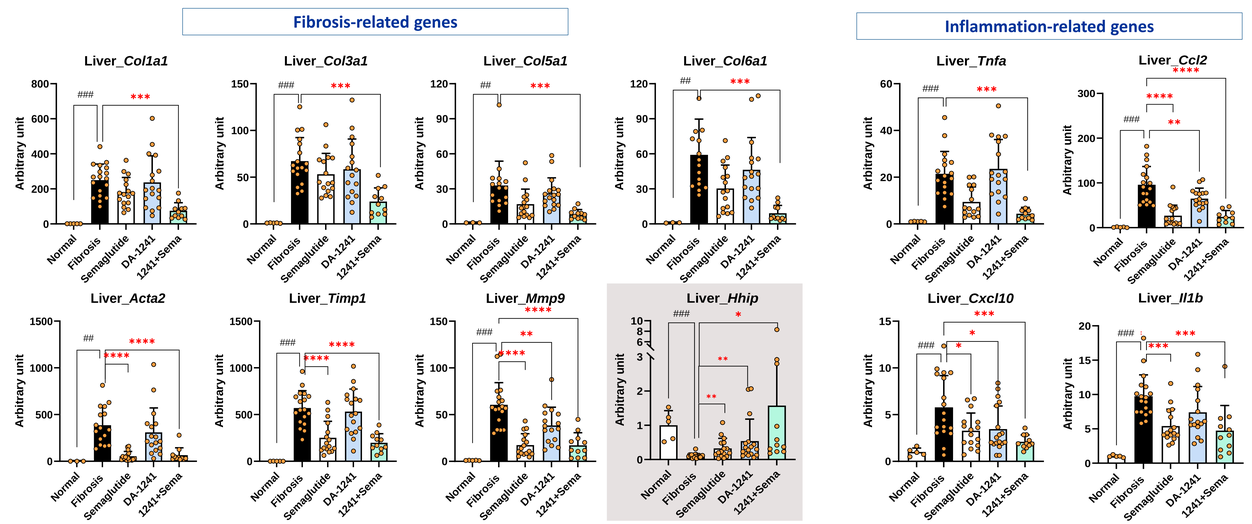


Results

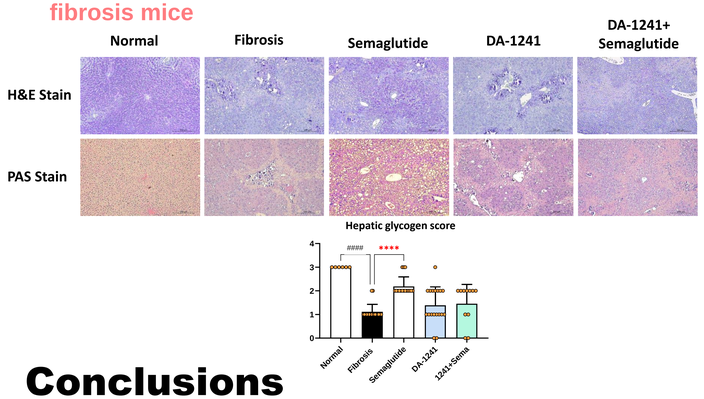
1. Synergistic anti-fibrosis effects by DA-1241 combined with Semaglutide in liver fibrosis mice



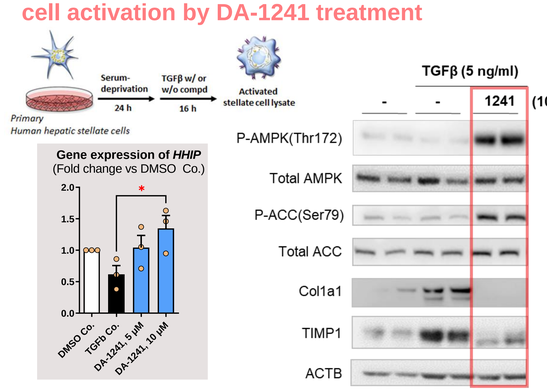
2. Enhanced improvement of fibrotic and inflammatory gene expression in the combination group



3. Differential effects on hepatic glycogen content in liver fibrosis mice



4. Direct inhibition of human primary hepatic stellate cell activation by DA-1241 treatment



Conclusions

- Our findings support a beneficial combination effect of DA-1241 and semaglutide in the treatment of liver fibrosis, which may be attributed to augmented inhibition of fibrogenesis and inflammation[1)] in the liver.
- DA-1241 has been proven to have compensatory anti-MASH effects with GLP1-based drugs in addition to DPP4 inhibitors.

References

[1)] **Kim M-K et al.**, GPR119 activation by DA-1241 alleviates hepatic and systemic inflammation in MASH mice through inhibition of NFκB signaling. *Biomed Pharmacother 2023;116:115345*

Linked Poster Presentation

Please visit **[THU-232] poster presentation** titled 'Additive hepatoprotective effects of DA-1241, a novel GPR119 agonist, in combination with semaglutide in the GAN diet-induced obese and biopsy-confirmed mouse model of MASH'