FGF19 Gene Therapy Reduces Steatosis but not Inflammation and Fibrosis in Two Mouse Models of NASH

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Background

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of liver disease ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) and cirrhosis. No treatment has been approved for NASH.

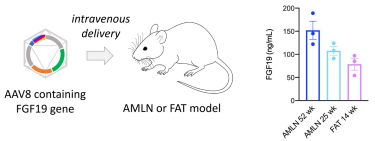
Fibroblast growth factor 19 (FGF19) is an endocrine hormone produced in the ileum in an Farnesoid X receptor (FXR)-dependent manner. FGF19 and non-tumorigenic analogues, such as the variant M70, have been shown to reduce steatosis, inflammation, and fibrosis in preclinical models of NASH. However, despite promising results in early Phase II, recombinant M70 (Aldafermin, NGM BioPharma) recently failed to reduce fibrosis in Phase IIb trials.

AAV gene therapy has recently been FDA approved for two disorders and is a one-shot alternative to repeated dosing of recombinant protein. **We tested the therapeutic efficacy of AAV expressing FGF19 in two mouse models NASH.**

Methods

AAV serotype 8 was produced expressing FGF19 (M70) and a non-therapeutic control, green fluorescent protein (GFP) and intravenously administered to two NASH models.

a) AMLN: High-fat, high-fructose, high-cholesterol diet
b) FAT: As above + weekly injections of CCl4



Two studies were conducted; a 2-month FGF19 treatment and a 3-month FGF19 treatment:

2-month cohort

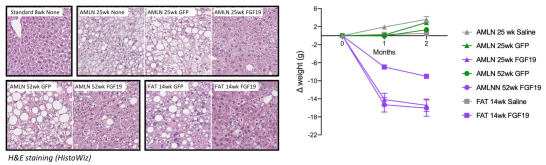
Saline	Standard chow
Saline	AMLN 25wk (low-fibrosis)
AAV:GFP	AMLN 25wk (low-fibrosis)
AAV:FGF19	AMLN 25wk (low-fibrosis)
AAV:GFP	AMLN 52wk (high-fibrosis)
AAV:FGF19	AMLN 52wk (high-fibrosis)
Saline	FAT 14wk (high-fibrosis)
AAV:FGF19	FAT 14wk (high-fibrosis)

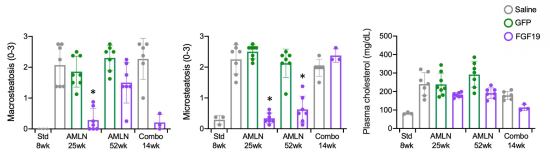
3-month cohort

Saline	Standard chow
AAV:GFP	AMLN 29wk (mid-fibrosis)
AAV:FGF19	AMLN 29wk (mid-fibrosis)

Results

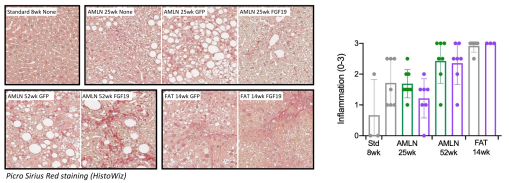
1. Two months of FGF19 therapy reduces weight and steatosis in AMLN and FAT mice

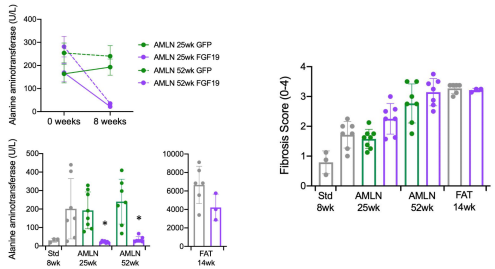




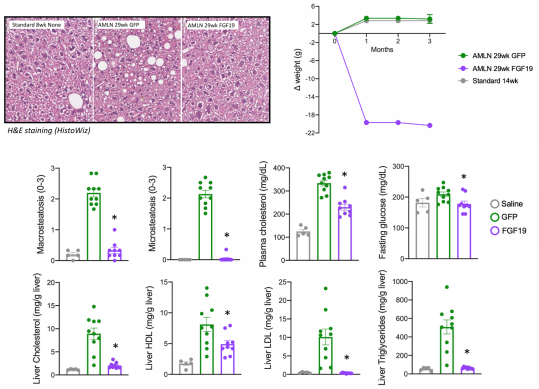
* P<0.05 (two-tailed t-test vs GFP control)

2. Reduction in ALT, but not inflammation or fibrosis at two months in both models

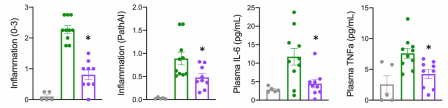




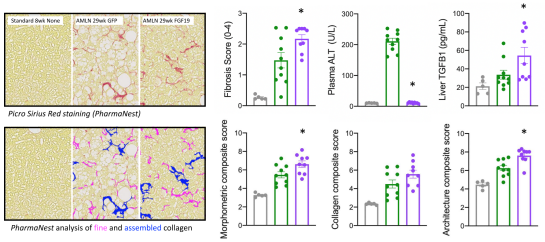
3. Three months of FGF19 therapy also has marked reduction in steatosis in AMLN mice



4. In contrast to two months, longer treatment decreases inflammatory markers and histology



5. Three months of treatment duration increases fibrosis markers and histology



Conclusions

2 months of FGF19 therapy reduces steatosis and ALT levels, but not inflammation or fibrosis in AMLN and FAT mice.

3 months of FGF19 therapy reduces steatosis, inflammation and ALT levels, but not fibrosis in AMLN mice. Interestingly, collagen levels and fibrosis phenotypic scoring indicated *increased* fibrosis in treated tissues after 3 months.

Our findings support observations made in the NGM Phase IIb trial, suggesting that short-term treatment of FGF19 does not reduce fibrosis.

Acknowledgements

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Disclosures

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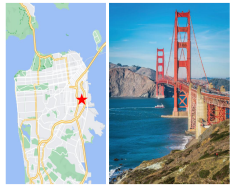

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