Aldafermin (NGM282) reduces the cross-linked pro-peptides of type III collagen Pro-C3X, a novel biomarker, in non-alcoholic steatohepatitis and primary sclerosing cholangitis patients

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INTRODUCTION

- Cross-linking of collagen is a key contributor to tissue stiffness. Not only the amount and pattern of fibrillar collagens, but also the plasticity to change, are important during fibrosis progression and reversal.
- The novel biomarker Pro-C3X specifically detects the cross-linked pro-peptides of type III collagen. Recent studies have shown that circulating concentrations of Pro-C3X are elevated in HCC patients, and are superior to Pro-C3 in predicting progression-free survival and overall survival independent of AFP.
- Aldafermin (NGM282), a non-tumorigenic FGF19 analogue, is a potent regulator of bile acid synthesis with anti-fibrotic effects in clinical trials.
- We determined plasma levels of Pro-C3X in phase 2 trials of aldafermin in NASH and PSC.

AIM

- We aimed to investigate the effect of aldafermin on the novel biomarker, Pro-C3X, in patients with NASH or PSC enrolled in aldafermin phase 2 trials.

METHOD

- 43 NASH subjects, with NAS ≥4 (at least 1 point in each component), stage 1-3 fibrosis and absolute liver fat content by MRI-PDF, 28% received aldafermin 1mg or 3mg daily for 12 weeks.
- 62 PSC subjects, with an elevated ALP+ 5xULN at baseline (BL), received aldafermin 1mg, 3mg or placebo daily for 12 weeks.
- The Pro-C3X sandwich ELISA only detects cross-linked type III collagen pro-peptides (Nordic Bioscience).
- Pro-C3 competitive ELISA quantifies the sum of single-stranded and cross-linked pro-peptides (Nordic Bioscience).

RESULTS

- At baseline, circulating Pro-C3X concentrations were significantly lower in subjects with NASH than PSC (9.1 ng/mL vs 14.7 ng/mL), while Pro-C3 levels were similar in NASH and PSC.
- Lower Levels of Cross-Linked Type III Collagen in NASH than in PSC.

CONCLUSIONS

- The novel biomarker Pro-C3X detects cross-linked pro-peptides of type III collagen, and has the potential to differentiate the different collagen characteristics beyond histology.
- NASH patients had much lower type III collagen cross-linking than PSC patients, indicating that the collagens in NASH may be more plastic and malleable than collagen III thought.
- Aldafermin significantly reduces Pro-C3X, a novel noninvasive marker of cross-linked type III collagen, in both NASH and PSC populations.
- These results further support the rapid fibrosis reversal with aldafermin therapy in a dynamic extracellular matrix environment across metabolic and cholestatic liver disease.

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