CONCLUSIONS

Aldafermin 3 mg

Patient #3 (3 mg)
in Patients with Primary Sclerosing Cholangitis

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INTRODUCTION

- Pruritus is a common symptom in patients with cholestatic liver diseases, including primary sclerosing cholangitis (PSC), an inflammatory and progressively fibrotic liver disease devoid of effective medical interventions
- The pathogenesis of pruritus is poorly understood, and proposed pruritogens include bile acids and autotaxin/lysophosphatidic acid 1-3
- Recently, bile acids have been shown to activate the MRGPRX4 receptor located in the sensory neurons to induce itch 10
- Aldafermin (NGM282), a non-tumorigenic FGF19 analogue, potently inhibits bile acid synthesis, improves hepatic inflammation, and decreases fibrosis markers in patients with PSC 4

AIM

- To determine whether certain bile acid species may be related to pruritus, we correlated changes in individual serum bile acids with patient-reported outcome measures of pruritus from a phase 2 aldafermin trial in patients with PSC

METHOD

- 62 subjects, with PSC by EASL criteria and an elevated ALP>1.5xULN at baseline (BL), were randomized to daily aldafermin 1mg, 3mg or placebo (PBO) for 12 weeks (W12)
- 5D-itch pruritus questionnaires (scores from 5 to 25) and fatigue severity numeric rating scale (NRS, from 0 to 10) were collected; higher numbers indicated more severe symptoms
- Serum concentrations of bile acid species were determined by mass spectrometry (Mayo Clinic)
- Scores were compared with the use of a mixed-effect model repeated measures analysis
- Correlations between pruritus and serum bile acids were assessed with a clinical anchor threshold of >0.30 and P <0.05 as significant

RESULTS

- At baseline, pruritus severity by 5D-itch correlated with serum concentrations of GCA and TCA, but not ALP, ALT, AST, C4 or ELF
- Reductions from baseline in GCA and GCDCA were observed in the aldafermin groups, but not in the placebo group
- Aldafermin groups had less robust reductions in TCA and TCDCA
- Reductions from baseline in GCA and TCA, but not ALP, ALT, AST, C4 or ELF
- At week 12, aldafermin treatment was associated with a trend of improvement in pruritus and fatigue, especially in the 3 mg group
- Correlations between pruritus and serum bile acids were assessed with a clinical anchor threshold of >0.30 and P <0.05 as significant

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REFERENCES

1. Meixiong et al., MRGPRX4 is a G protein-coupled receptor activated by bile acids that may contribute to cholestatic pruritus. Proc Natl Acad Sci USA 2019;116:10526-10530.