Bile Acids and Liver Fibrosis: Shared Anti-Fibrotic Effects of NGM282 (Aldafermin), an FGF19 Analogue, in Primary Sclerosing Cholangitis and Non-Alcoholic Steatohepatitis

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CONCLUSION

Pro-C3 in Pooled PSC and NASH Populations

- Changes in circulating levels of bile acids highly correlated with changes in the fibrogenesis marker Pro-C3 in patients treated with aldafermin.
- Dysregulated bile acid homeostasis appears to be a shared molecular mechanism, and therapeutic target, underlying fibrosis and disease progression across cholestatic and metabolic liver disease.

Aldafermin Lowers Serum Bile Acids Irrespective of Disease Etiology

- Administration of aldafermin produced dose-dependent reductions in bile acid species, and the more toxic, hydrophilic, glyco-conjugated bile acids in particular (i.e., GCA, GCDCA, GDCA), across patient subgroups with PSC or NASH.
- Pro-C3 levels (a biomarker of disease activity and fibrosis) in both PSC and NASH patients decreased significantly after aldafermin treatment.
- In contrast, no significant decrease in Pro-C3 was observed in placebo-treated patients.

Correlation in Pooled PSC and NASH Populations

- In the pooled analysis (PSC and NASH populations), bile acid species strongly correlated with the fibrogenesis marker Pro-C3 at baseline and Week 12.
- Percent changes from baseline to Week 12 in Pro-C3 correlated with percent changes in bile acids (i.e., GCA, GCDCA, GDCA, TCA).

METHODS

- Comparison of Baseline Serum Bile Acids in PSC and NASH
- At baseline, patients with PSC had markedly elevated bile acids compared to patients with NASH.
- Levels of glucuronolactone conjugated bile acids were significantly higher in patients with PSC than NASH.
- Independent effects of aldafermin on lowering serum bile acids were observed in both PSC and NASH patients.

Correlation Between Changes in Bile Acids and Pro-C3

- Changes in circulating levels of bile acids highly correlated with changes in the fibrogenesis marker Pro-C3.
- Pro-C3 levels (a biomarker of disease activity and fibrosis) in both PSC and NASH patients decreased significantly after aldafermin treatment.
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PSC NASH P value

Conjugated Primary Bile Acids

GCA (μmol/L) 8.9 0.4 <0.0001
TCA (μmol/L) 5.0 0.1 <0.0001
GDCA (μmol/L) 12.0 1.5 <0.0001
TDCDA (μmol/L) 4.2 0.2 <0.0001

Conjugated Secondary Bile Acids

GCDCA (μmol/L) 0.3 0.02 <0.0001

TCA (μmol/L) 0.5 0.3 0.0028

Unconjugated Primary Bile Acids

CA (μmol/L) 0.17 0.21 0.25

BGCA (μmol/L) 0.21 0.04 0.0016

Unconjugated Secondary Bile Acids

DCA (μmol/L) 0.20 0.75 <0.0001

Percentage changes from baseline to Week 12 in Pro-C3 correlated with

<table>
<thead>
<tr>
<th>Bile Acid</th>
<th>Week 12 PSC</th>
<th>Week 12 NASH</th>
<th>P value</th>
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<td>GCA</td>
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<tr>
<td>TDCDA</td>
<td>0.01 0.01  0.02</td>
<td>0.01 0.01  0.02</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

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