Liver sinusoidal endothelial cell (LSEC) capillarization in NASH and its evolution following lanifibranor treatment: an exploratory study of the NATIVE clinical trial

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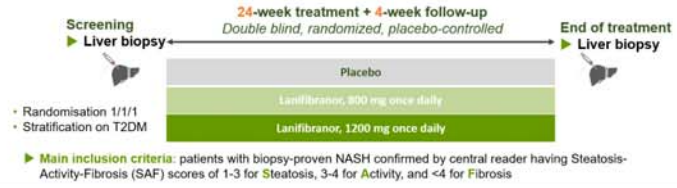
1-INTRODUCTION

Liver sinusoidal endothelial cell (LSEC) are specialized endothelial cells which are permeable because of their fenestrae and lack of basal membrane. LSECs maintain hepatocyte homeostasis, hepatic stellate cell quiescence and hepatic vascular tone contributing to maintenance of low portal pressure. LSEC capillarization in chronic liver disease has been associated with increased hepatic fibrosis and portal pressure. Limited clinical studies showed that LSEC capillarization occurs at early stages of NASH. Preclinical models suggest that this change contributes to steatosis, liver inflammation and fibrosis. We here report the results of an exploratory study using trial liver biopsies specimens obtained during the NATIVE study, to determine: (a) histological features of NASH associated with LSEC changes, measured by liver CD34 expression, a marker of LSEC capillarization; (b) whether LSEC changes can regress with lanifibranor.

2-MATERIAL/METHODS

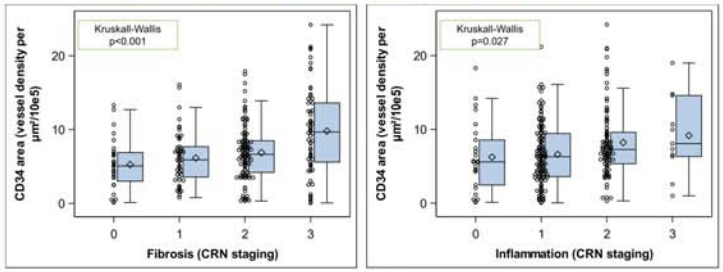
NATIVE was a phase 2b double-blind randomised-controlled trial of lanifibranor, a pan-PPAR agonist, in patients with non-cirrhotic NASH, with activity (A) ≥3 according to SAF score. Patients were randomised 1:1:1 to receive placebo, 800 or 1200 mg of lanifibranor daily for 24 weeks. Biopsies were taken at baseline and at end of treatment (EOT); we assessed (a) the features of NASH associated with LSEC changes using liver biopsies performed at baseline in 249 patients considered for inclusion in NATIVE; (b) the evolution of LSEC changes following lanifibranor treatment in liver biopsies of 162 patients included in NATIVE. CD34 immunostaining was quantified by morphometric analysis (using dedicated algorithm of microvessel density Imagescope APerio) and by 2 semi-quantitative scores (centrilobular and periportal, defined as 0=0%, 1/3:< 33%, 2/3: 33-66% and 3/3: >66% of the lobular surface). CD34 and ERG costaining was performed on 20 slides and ensured endothelial specificity of CD34 staining.

NATIVE study design



3-RESULTS

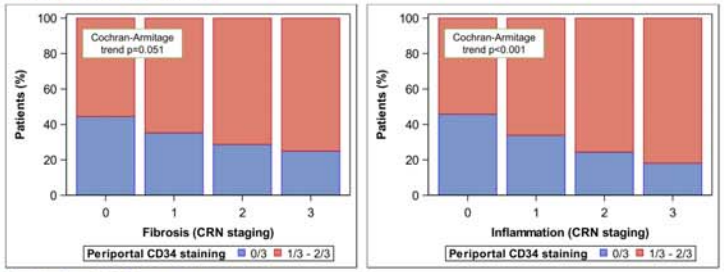
Morphometric CD34 and histological features of NASH



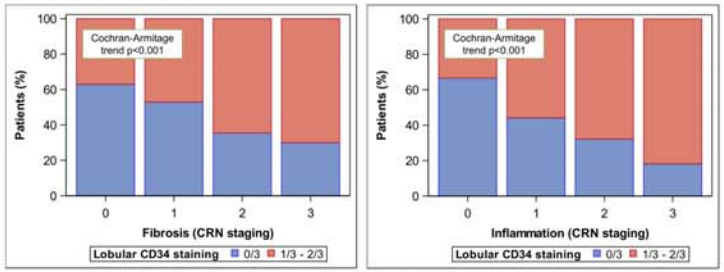
CD34 staining, assessed by morphometry, was strongly associated with liver fibrosis and to a lesser extent with lobular inflammation, but not with steatosis or hepatocellular ballooning (data not shown).

Semi-quantitative CD34 scoring and features of NASH

Periportal CD34 score

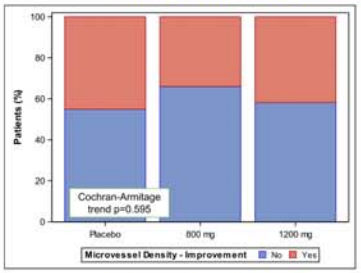


Lobular CD34 score



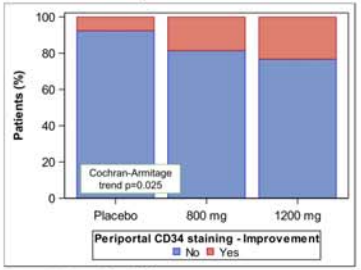
Semi-quantitative scores for CD34 staining were associated with liver fibrosis and lobular inflammation.

Treatment effect of lanifibranor versus placebo

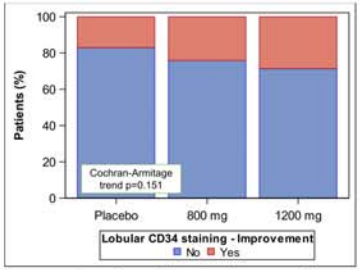


No difference between active groups and placebo regarding improvement in CD34 staining by morphometry (defined as a decrease of 20% compared to baseline).

Periportal CD34 score



Lobular CD34 score



At EOT, lanifibranor treatment was associated with a lower, dose-dependent, expression of CD34: this difference was significant in the periportal area, but not in the centrilobular area.

4-CONCLUSION

In patients with NASH, LSEC capillarization (i.e. CD34 expression) increases with liver fibrosis and lobular inflammation, but not with steatosis or ballooning. Lanifibranor treatment is associated with a dose-dependent reduction of CD34 staining which reached statistical significance in periportal area. Whether this effect of lanifibranor is due to a direct effect on endothelial cells or a consequence of its anti-inflammatory and anti-fibrotic activity will require further studies.

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