The Liver Fibroinflammatory Marker cT1 is Reduced with Aldafermin Therapy in a Randomized, Double-Blind, Placebo-Controlled, Multicenter Study in Patients with Nonalcoholic Steatohepatitis

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Abstract 985 (EASL 2021)

INTRODUCTION

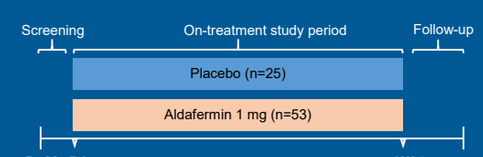
- The iron-corrected T1 relaxation time (cT1) is a novel imaging marker of intrahepatic fibro-inflammatory activity and is used in the UK Biobank population health study as the reference for liver fibroinflammatory disease [1]
- A threshold of cT1 >825ms has been shown to predict clinical outcomes (ascites, variceal bleeding, hepatic encephalopathy, hepatocellular carcinoma, liver transplantation, mortality; hazard ratio of 9.9, P=0.007) [2]
- In contrast, liver fat content, as measured by MRI-PDFF, is not predictive of clinical outcomes
- Aldafermin, an engineered FGF19 analog, produced fibrosis regression and NASH resolution in a 24-week, randomized, double-blind, placebo-controlled trial in patients with NASH [3]
- Here we report the effect of aldafermin on the novel imaging marker cT1 in this trial

AIM

To evaluate change in cT1 in a randomized, double-blind, placebo-controlled, 24-week study of aldafermin in patients with NASH

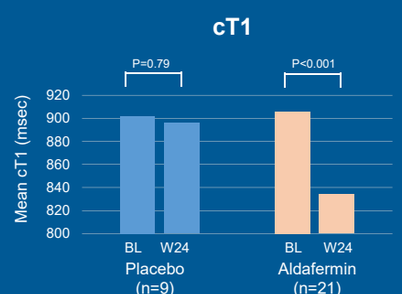
METHOD

- 78 subjects were randomized 1:2 to receive placebo (n=25) or aldafermin 1mg (n=53) SC QD for 24 weeks at 9 US study sites [3]
- Key inclusion criteria included biopsy-proven NASH with NAS≥4, F2 or F3 fibrosis and absolute liver fat content ≥8%
- Patients underwent the LiverMultiScan™ acquisition protocol (Perspectum Diagnostics) at baseline (BL) and week 24 (W24)
- cT1 maps were obtained on multiparametric magnetic resonance imaging scanners standardized across field strengths and vendors [4]
- Images were analyzed by trained central readers blinded to treatment assignment, clinical and histological information
- Because LiverMultiScan™ was not available at some study sites, overall 30 patients (9 and 21 in the placebo and aldafermin groups, respectively) had evaluable cT1 maps at both baseline and week 24 and were included in this analysis

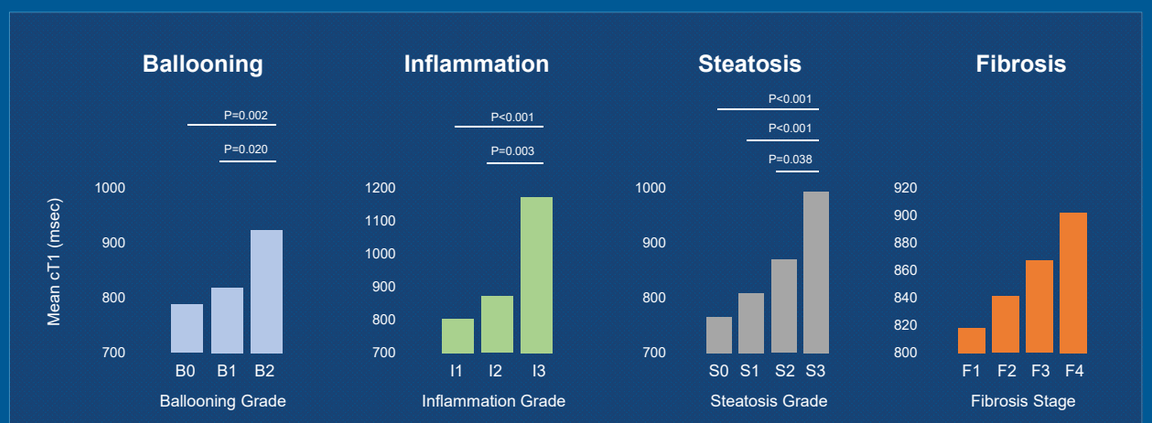


RESULTS

- *At baseline, mean cT1 values were 906msec and 902msec in the aldafermin and placebo groups, respectively*
- *At week 24, cT1 values declined significantly in aldafermin-treated subjects. In contrast, no change in cT1 was observed in placebo-treated subjects (difference in LS mean, −86 msec, P=0.03 vs placebo)*

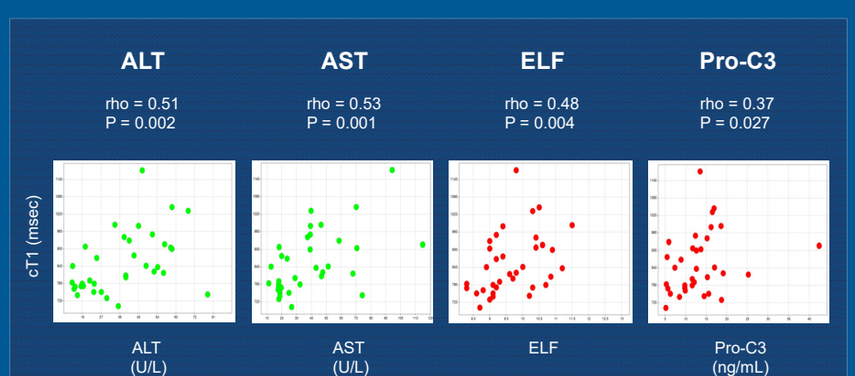


Correlation Between cT1 and Liver Histology



cT1 correlated with histological grades of ballooning, inflammation and steatosis at week 24.
A trend of correlation between cT1 and fibrosis stage was observed, but statistical significance was not reached.
Among subjects who achieved cT1 reduction of >=88msec, 64% achieved NAS reduction of 2 points or more, 91% achieved NAS reduction of 1 point or more, and 36% achieved fibrosis improvement of 1 stage or more with no worsening in NASH.

Correlation Between cT1 and Serum Markers



cT1 correlated with ALT (rho=0.51, P=0.002), AST (rho=0.53, P=0.001), ELF (rho=0.48, P=0.004) and Pro-C3 (rho=0.37, P=0.027) at week 24. Correlation coefficients were calculated using Spearman's method.

CONCLUSIONS

- Compared to placebo, aldafermin demonstrated significant reductions in cT1 values, consistent with its anti-inflammatory and anti-fibrotic effect on the NASH liver
- cT1 correlated with histological grades of ballooning, inflammation and steatosis, as well as non-invasive measures including ALT, AST, ELF and Pro-C3, at week 24
- cT1 may be used as a tool to follow patients over time to assess response to treatment and disease progression
- Given the prognostic value of cT1 on clinical outcomes, aldafermin treatment may provide benefits to the at-risk patient population defined as having cT1 >825ms

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EASL/ILC Conference, June 23-26, 2021
Amsterdam, Netherlands