Hepatic Fat Changes after an Antisense Oligonucleotide Therapy Targeting ANGPTL3

A TRANSLATE-TIMI 70 Analysis

André Zimerman, Stephen D. Wiviott, Jeong-Gun Park, Sabina A. Murphy, Xinhui Ran, Candace R. Bramson, Madelyn Curto, Vesper Ramos, Alexandra Jevne, Julia F. Kuder, Subodh Verma, Wojtek Wojakowski, Steven G. Terra, Marc S. Sabatine, Brian A. Bergmark*, Nicholas A. Marston*

TIMI Study Group, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (A.Z., S.D.W., J.-G.P., S.A.M., X.R., A.J., J.F.K., M.S.S., B.A.B., N.A.M.). Pfizer, Inc, New York, NY (C.R.B., M.C., V.R., S.G.T.). Department of Surgery, University of Toronto, Canada (S.V.). Medical University of Silesia, Katowice, Poland (W.W.). *B.A.B. and N.A.M. contributed equally.

BACKGROUND

Vupanorsen is a GalNAc-conjugated antisense oligonucleotide targeting angiopoietin-like 3 (ANGPTL3) protein that reduced triglycerides (TG) up to 57% but increased hepatic fat fraction (HFF), as assessed by hepatic MRI PDFF. The increase in HFF in different subtypes of patients and the relationship to liver function tests (LFT) remains undefined.

METHODS

227 patients with HFF measurements from the TRANSLATE-TIMI 70 trial completed 24-week follow-up and were included in this analysis. Patients were randomized to placebo or 1 of 7 vupanorsen regimens. We evaluated (1) change in HFF by arm, (2) subgroups at risk for HFF progression, and (3) the correlation between change in LFTs and HFF from baseline to 24 weeks.

RESULTS

- Median HFF at baseline was 8.5%. Median TG level was 216 mg/dL. 114 patients (50.2%) had diabetes.
- Vupanorsen led to progression in HFF ranging from 5% to 76% from baseline in a dose-dependent fashion (p<0.001) (**Figure 1**).
- Although there was no statistically significant heterogeneity, patients with higher baseline TG, HFF, and those with diabetes had numerically greater increases in HFF with vupanorsen (**Figure 2**).
- Increases in LFTs were significantly correlated with increased HFF (Spearman's rho = 0.45 for AST, 0.48 for ALT, both p < 0.001) (**Figure 3**).

CONCLUSION

Vupanorsen caused increases in HFF that were associated with dose of drug and increased LFTs. HFF may be important to evaluate for future therapies targeting triglyceride-rich lipoproteins, especially those that work intracellularly.

Vupanorsen caused **increases in hepatic fat fraction** that were dose-dependent and correlated with increased liver function tests.

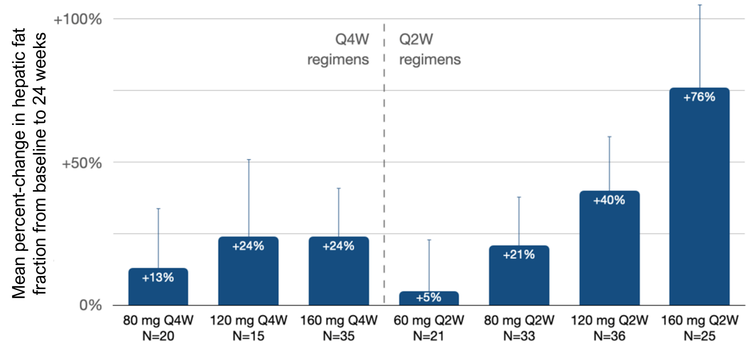
Hepatic fat may be important to evaluate for future therapies targeting triglyceride-rich lipoproteins, especially those that work intracellularly.

For more information, contact
azimerman@bwh.harvard.edu
or @AndreZimerman

ACC.23 TOGETHER WITH WCC

FIGURE 1

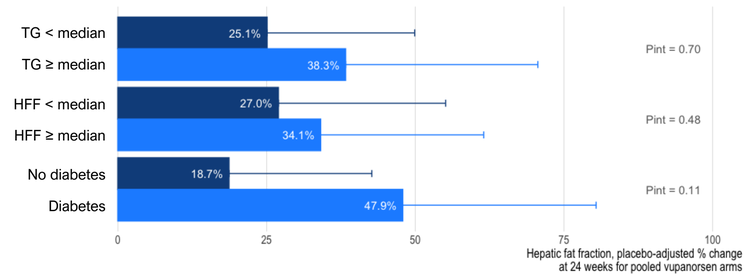
Effect of vupanorsen on hepatic fat fraction at 24 weeks by treatment arm



*Error bars indicate 95% confidence intervals. Percent-change for placebo group was -1%, not displayed.

FIGURE 2

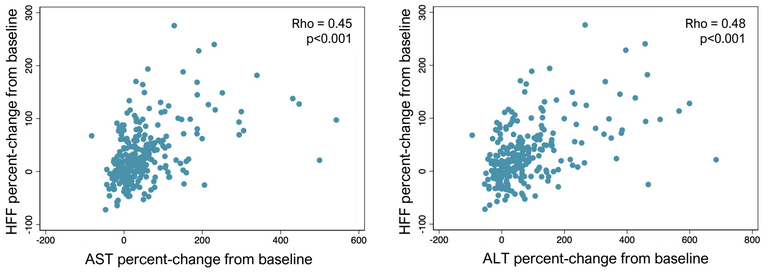
Effect of vupanorsen on hepatic fat fraction at 24 weeks in key subgroups



*Error bars indicate 95% confidence intervals.

FIGURE 3

Correlation between changes in liver function tests and hepatic fat fraction from baseline to 24 weeks



DISCLOSURES

Dr. Zimerman reports receiving a research scholarship from the Lemann Foundation. Dr. Marston reports receiving presentation fees from Amgen; nonfinancial support from Ionis and Pfizer; grants from the National Institutes of Health; and participating in clinical trials with Amgen, Pfizer, Novartis, and AstraZeneca without personal fees, payments, or increase in salary.