Sustained Elevation in Alkaline Phosphatase is Associated with Greater Disease Severity in Real World NAFLD in TARGET–NASH

Andrew deLemos[1], A. Sidney Barritt[2], Kalyan Ram Bhamidimarri[3], Charles Landis[4], Laura Malahias[5], Miguel Malespin[6], Cheryl Schoen[5], Jawahar Taunk[7], Paul Thuluvath[8], Huy Ngoc Trinh[9], Brent A. Neuschwander–Tetri[10]

[1]Division of Hepatology, Carolinas Medical Center, Charlotte, NC [2]Division of Gastroenterology and Hepatology, University of North Carolina at Chapel Hill, UNC Liver Center, Chapel Hill, NC [3]Division of Hepatology at the University of Miami Miller School of Medicine, Miami, FL [4]Division of Gastroenterology and Hepatology, Department of Medicine, University of Washington, Seattle, WA [5]TARGET PharmaSolutions, Inc., Chapel Hill, NC [6]Division of Gastroenterology and Hepatology, Department of Medicine, University of Florida Health, Jacksonville, FL [7]Advanced Gastroenterology Associates, LLC, Palm Harbor, FL [8]Mercy Medical Center, Baltimore, MD [9]San Jose Gastroenterology, San Jose, CA [10]Division of Gastroenterology and Hepatology, Saint Louis University, St. Louis, MO

INTRODUCTION

- Nonalcoholic fatty liver disease (NAFLD) is highly prevalent in both children and adults.
- The overall aim of TARGET–NASH is to determine the natural history of NAFLD and to evaluate treatment regimens used in usual clinical practice.
- The aim of the current analysis is to evaluate the relationship between sustained elevation in alkaline phosphate (ALP) and disease severity across the NAFLD spectrum.

METHODS

- TARGET–NASH is a longitudinal observational study of participants followed at 55 sites (41 academic/14 community) in the U.S., and includes patients across the entire spectrum of NAFLD.
- Data from medical records (including narratives, labs, imaging, pathology, procedures, and outcomes) are centrally abstracted and monitored for completeness and accuracy.
- Of the 3,970 participants enrolled in TARGET–NASH, this analysis included 1,756 subjects who had ≥2 values of ALP for analysis.
- Participants were grouped by disease severity (NAFL, NASH, NAFLD cirrhosis) as defined by pragmatic case definitions.
- A sustained elevated ALP level was defined as 2 consecutive values >1.5*ULN (ULN=125 IU/L), while a non–elevated ALP level required all values ≤1.5*ULN. Participants with <2 ALP values were excluded from the analysis.
- Clinical variables and outcomes of subjects with sustained elevated ALP were compared to those with non–elevated ALP among the three disease severity groups.

DISEASE CATEGORY DEFINITIONS

NASH	Confirmed by biopsy: • Steatohepatitis by Brunt criteria OR NAS total score ≥ 4 Clinical diagnosis: • ALT > 19 U/L for adult female (22 child), > 30 U/L for adult male (26 child) and; • Hepatic steatosis on biopsy or CT/US/MRI and; • ≥ 1 of the following: BMI ≥ 30, type II diabetes, dyslipidemia
NAFLD Cirrhosis	History of NAFLD with: 1) Liver biopsy with fibrosis stage = 4 OR 2) Liver biopsy with fibrosis stage = 3 and 1 ≥ clinical signs of cirrhosis OR 3) 2 or more clinical signs of cirrhosis OR 4) FibroScan® elastography result ≥ 11 kPa
NAFL	Any participant not meeting criteria for clinical NASH or cirrhosis

RESULTS

Sustained ALP Elevation and Risk Factors for Disease Severity in Adult TARGET–NASH Participants (N=1756)

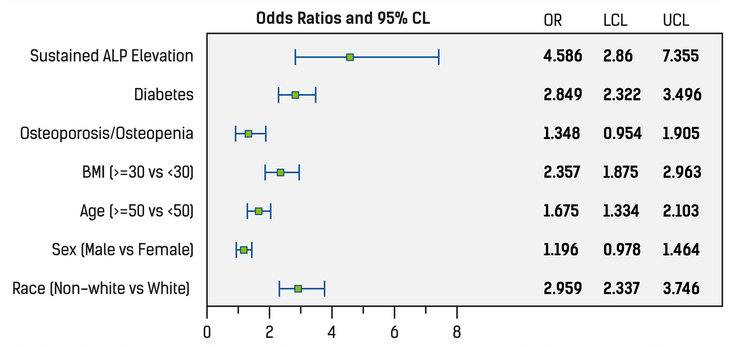
SUMMARY	NAFLD Cirrhosis		NASH		NAFL	
	Sustained Elevated ALP (N=88)	**No Elevated ALP (N=597)**	**Sustained Elevated ALP (N=24)**	**No Elevated ALP (N=699)**	**Sustained Elevated ALP (N=3)**	**No Elevated ALP (N=345)**
Age at Study Entry (years) Median (n)	**61.0 (88)**	**63.0 (596)**	**58.0 (24)**	**56.0 (699)**	**48.0 (3)**	**59.0 (343)**
Gender (%) Female Male	**64.8** **35.2**	**57.6** **42.4**	**87.5** **12.5**	**59.1** **40.9**	**33.3** **66.6**	**50.1** **49.9**
Race (%) White	**83.0**	**86.7**	**91.7**	**67.1**	**100.0**	**46.7**
BMI (kg/m^2) (%) <30 >=30	**20.9** **79.1**	**19.0** **81.0**	**8.7** **91.3**	**23.0** **77.0**	**33.3** **66.7**	**60.5** **39.5**
Alkaline Phosphatase (IU/L)[1] Median (n)	**192.6 (88)**	**87.5 (597)**	**198.2 (24)**	**76.2 (699)**	**196.0 (3)**	**71.2 (345)**
Diabetes (%) No Yes	**25.0** **75.0**	**32.3** **67.7**	**62.5** **37.5**	**56.2** **43.8**	**100.0** **0**	**74.8** **25.2**
Osteoporosis or Osteopenia (%)[2] No Yes	**89.8** **10.2**	**88.9** **11.1**	**83.3** **16.7**	**90.6** **9.4**	**100.0** **0**	**92.8** **7.2**
MELD Score[3] Median (n)	**14.0 (85)**	**9.0 (505)**	**7.0 (15)**	**7.0 (328)**	**13.0 (2)**	**7.0 (88)**
Any Decompensating Event (%) No Yes	**34.1** **65.9**	**64.7** **35.3**	**100.0** **0**	**98.7** **1.3**	**100.0** **0**	**99.4** **0.6**

[1] Average of all available ALP values.

[2] Osteoporosis or osteopenia as indicated in participant medical history, adverse events or reported use of bisphosphonate.

[3] MELD Score is derived at visits where creatinine, total bilirubin and INR are all non–missing. The MELD Score summarized is a participant's worst available MELD Score.

Risk Indicators for Disease Severity



Note: ORs and CLs are from a forward, step–wise logistic regression model (significance level for entry=.25, significance level to remain in the model=0.1) fit with the following predictors of disease severity: sustained ALP elevation, osteoporosis/osteopenia, age at enrollment (dichotomous response), race (dichotomous response), sex BMI at enrollment (dichotomous response) and diabetes. The final model includes the following risk indicators for disease severity: diabetes, race, BMI at enrollment (dichotomous response), sustained ALP elevation, age at enrollment (dichotomous response), sex and osteoporosis/osteopenia.

SUMMARY & CONCLUSIONS

- The study population comprised 115 participants with sustained elevated ALP, 88 (77%) NAFLD cirrhosis (median ALP=192.6 IU/L), 24 (21%) NASH (median ALP=198.2 IU/L), and 3 (2%) NAFL (median ALP=196.0 IU/L) and 1,641 with non–elevated ALP, 597 NAFLD cirrhosis (36%, median ALP=87.5 IU/L), 699 NASH (43%, median ALP=76.2 IU/L), and 345 NAFL (21%, median ALP=71.2 IU/L).
- The sustained elevated ALP group with NAFLD cirrhosis had a higher MELD score (14 vs 9) and more decompensating events (66% vs 35%) compared to the non–elevated ALP group with NAFLD cirrhosis.
- There was no difference in age, gender, or osteoporosis/osteopenia among the same two groups.
- In the TARGET–NASH population, 7% of participants have sustained elevated ALP. This group is more likely to have cirrhosis and among those with cirrhosis have higher MELD scores and a higher likelihood of decompensating events compared to those with non–elevated ALP
- Sustained elevated ALP was independently associated with increased disease severity and this correlation persisted after including known risk factors for disease progression such as diabetes and obesity.

STATEMENT & DISCLOSURES

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