AASLD The Liver Meeting®

COMPLICATION-FREE SURVIVAL IN A REAL-WORLD COHORT OF PBC PATIENTS: DEEP VERSUS ADEQUATE ALP RESPONSE TO UDCA

Anish Reddy[1], Dr. Christopher L. Bowlus[2], Dr. Marylyn J. Mayo[3], Dr. Elizabeth Carey[4], Dr. Andrea Mospan[5], Dr. Aparna Goel[6], Dr. Cynthia Levy[1]

1: University of Miami Miller School of Medicine, 2: University of California, Davis, 3: University of Texas Southwestern Medical Center, 4: Mayo Clinic Arizona, 5: Target RWE, 6: Stanford University School of Medicine

MIAMI

INTRODUCTION

- The current treatment paradigm for primary biliary cholangitis (PBC) is to begin second-line therapies if alkaline phosphatase (ALP) levels do not reach levels below 1.5-1.67x ULN [1], currently considered an adequate response
- Current research indicates that there may be a survival benefit to ALP normalization (a "deep" ALP response) compared to reaching ALP 1-1.5x ULN, and to reducing total bilirubin (TB) to ≤0.6x ULN (a "deep" bilirubin response), compared to TB 0.6-1xULN [2].

METHODS

- We analyzed data from TARGET-PBC, a longitudinal cohort of PBC patients receiving usual care and observed over 5 years across multiple sites in the US [3], sponsored by Target RWE.
- The eligibility criteria for the present study were the following: (1) recorded UDCA start date, (2) no second-line therapy at any point during treatment, (3) have met adequate response to UDCA according to Paris-2 criteria, and (4) no prior decompensating event.
- Patients were classified with advanced fibrosis status if they exhibited any of the following characteristics: LSM ≥ 10 kPa, cirrhosis diagnosis by liver biopsy, thrombocytopenia, evidence of esophageal varices or collateral circulation on imaging, or splenomegaly. Age was stratified into two groups: younger than 65 and 65 or older. This age cutoff was retrieved utilizing an ROC curve.
- The study collected data on serious clinical events, which included instances of cirrhosis decompensation (e.g. ascites, hepatic encephalopathy and variceal bleeding), LT, and death.
- The primary outcome of interest was complication-free survival, defined as the time from enrollment into either the deep or adequate response cohorts to the occurrence of a serious clinical event. Patients were censored after the first serious clinical event occurred.
- Kaplan-Meier survival curves were used to assess complication-free survival, with differences between the deep and adequate response groups compared using the log-rank test.
- Cox proportional hazards regression models were employed, with hazard ratios (HR) and 95% confidence intervals (CI) calculated to quantify the risk of clinical events.
- Restricted mean survival time (RMST) analysis was used to quantify the survival time gained in competing cohorts, with a cutoff of 222.5 months, as this as the latest data point available that fell within the groups being compared.

RESULTS

- The flowchart for patient selection is depicted in Figure 1 and their baseline characteristics are shown in Table 1
- The HR for meeting a serious clinical event was 0.34 [CI: 0.15 – 0.80] when comparing the deep ALP response group to the adequate ALP response group.
- The HR for meeting a serious clinical event was 0.23 [CI: 0.09 - 0.55] when comparing the deep TB response group to the adequate TB response group.
- Advanced fibrosis patients are large contributors to these hazard ratio differences, as these HRs are not significant in low-risk patients.
- There is a significant difference in mean complication-free survival time between both the deep ALP and adequate ALP groups, and the deep TB and adequate TB groups.

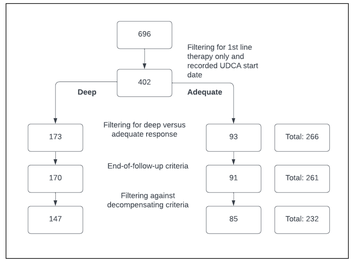

Figure #1: Flowchart of participants with associated inclusion and exclusion criteria.

	Adequate ALP response	N	Deep ALP response	N
Age, median [IQR]	61 (52,71)	85	66 (58,71)	147
≥ 65 years	43.53%	37	51.70%	76
Female gender	92.94%	79	93.88%	138
ALP at baseline*, mean (SD)	134.06 (53.13)	85	88.09 (37.64)	147
TB at baseline*, mean (SD)	0.62 (0.2539)	85	0.5265 (0.2091)	147
≤ 0.6 xULN	65.88%	56	82.31%	121
Advanced Fibrosis Patients**	55.29%	47	55.78%	82
UDCA therapy length in years, median [IQR]	6.08 (4.53, 8.38)	85	7.7 (6.24, 9.69)	147
LSM, median [IQR]	6.00 (4.65, 9.10)	7	5.95 (4.00, 6.90)	20
≥ 10kPa	14.29%	1	10.00%	2

Table #1: Demographics of included cohort. *ALP and bilirubin criteria for deep versus adequate responses were determined based on two consecutive measurements. The values analyzed here are those of the most recent of the two measurements at the time entry criteria was met into either a deep or adequate response. **Advanced fibrosis is defined as FibroScan® LSM > 10 kPa, or mention of cirrhosis, thrombocytopenia, varices, or splenomegaly in patient's medical records prior to meeting deep or adequate response.

	HR	Pr(>|z|)
Unadjusted analysis		
Alkaline Phosphatase (ALP) < ULN	0.39 [0.17, 0.90]	0.027
Bilirubin < 0.6 * ULN	0.18 [0.08, 0.42]	< 0.0001
Aspartate Transaminase < ULN	0.22 [0.10, 0.52]	< 0.001
Alanine Transaminase < ULN	0.72 [0.26, 1.95]	0.513
Platelets > LLN	0.17 [0.07, 0.39]	< 0.0001
Albumin > LLN	0.13 [0.05. 0.32]	< 0.00001
Adjusted (sex and binary age): All patients		
Alkaline Phosphatase (ALP) < ULN	0.34 [0.15, 0.80]	0.014
Bilirubin < 0.6 * ULN	0.23 [0.09, 0.55]	0.001
Adjusted (sex and binary age): Advanced fibrosis patients		
Alkaline Phosphatase (ALP) < ULN	0.24 [0.09, 0.65]	0.005
Bilirubin < 0.6 * ULN	0.25 [0.09, 0.68]	0.007

Table #2: Univariate and Multivariate Cox Proportional Hazard Model Results for Complication-Free Survival

Variable	RMST Difference (years)	p-value	RMST Ratio (Relative Gain)	p-value	RMTL Ratio (HR)	p-value
All patients: ALP response	1.34 [0.56, 2.11]	0.001	1.22 [1.07, 1.39]	0.003	0.13 [0.06, 0.31]	< 0.001
All patients: Bilirubin response	3.70 [3.11, 4.29]	< 0.001	1.99 [1.72, 2.30]	< 0.001	0.08 [0.04, 0.17]	< 0.001
Advanced fibrosis patients: ALP response	1.69 [0.58, 2.80]	0.003	1.30 [1.07, 1.60]	0.010	0.16 [0.07, 0.40]	< 0.001
Advanced fibrosis patients: Bilirubin response	3.52 [2.93, 4.38]	< 0.001	1.95 [1.61, 2.35]	< 0.001	0.13 [0.05, 0.30]	< 0.001

Table #3: Restricted Mean Complication-Free Survival Time Analysis of Different Cohorts

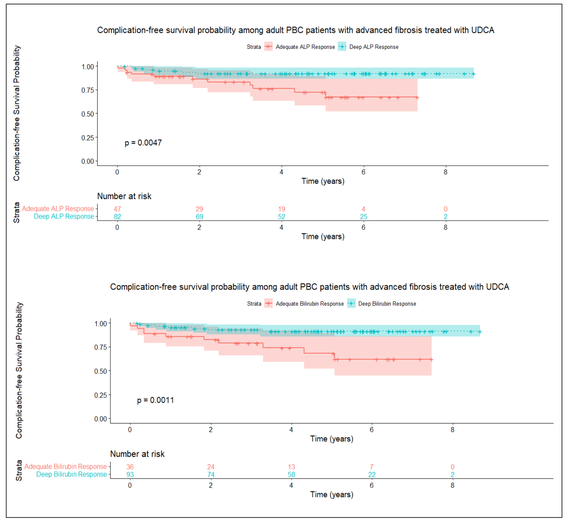

Figure #2: KM survival curve displaying complication-free survival probability of advanced fibrosis participants based on a deep or adequate ALP (top) or bilirubin (bottom) response.

CONCLUSIONS

- There was a significant decrease in the hazards of meeting serious complications and an increase in survival time free of these complications for cohorts that either met a deep ALP or deep bilirubin response.
- The impact of a deep response appears to be more pronounced in patients classified with advanced fibrosis.
- These findings suggest that patients with advanced fibrosis are likely to benefit from more aggressive therapy to achieve normalization of ALP and a deep bilirubin response.

REFERENCES

1. Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases. Hepatology. 2019;69(1):394-419.
2. Corpechot C, Lemoinne S, Soret PA, Hansen B, Hirschfield G, Gulamhusein A, et al. Adequate versus deep response to ursodeoxycholic acid in primary biliary cholangitis: To what extent and under what conditions is normal alkaline phosphatase level associated with complication-free survival gain? Hepatology. 2024;79(1):39-48.
3. Levy C, Bowlus CL, Carey E, Crawford JM, Deane K, Mayo MJ, et al. A real-world observational cohort of patients with primary biliary cholangitis: TARGET-primary biliary cholangitis study design and rationale. Hepatol Commun. 2018;2(5):484-91.

ACKNOWLEDGEMENTS

We would like to acknowledge Dr. Adrielly Martins for her significant support and guidance in this project.

CONTACT INFORMATION

Email: axr2735@med.miami.edu
Phone Number: 925-520-5945