Seladelpar Treatment of Patients With Primary Biliary Cholangitis (PBC) For 2 Years Improves the GLOBE PBC Score and Predicts Improved Transplant-Free Survival

THU461

Bettina E. Hansen[1,2,3], Elaine Watkins[4], Ke Yang[4], Yun-Jung Choi[4], Charles A. McWherter[4], Gideon M. Hirschfield[5]

1. Department of Epidemiology & Biostatistics, Erasmus MC, Rotterdam, the Netherlands, 2. Toronto Centre for Liver Disease, Toronto General Hospital, University Health Network, Toronto, Canada, 3. Institute of Health Policy, Management and Evaluation (IHPME), University of Toronto, Toronto, Canada, 4. CymaBay Therapeutics, Inc., Newark, CA, USA, 5. Toronto Centre for Liver Disease, University of Toronto, Toronto, Canada

EASL™ The Home of Hepatology
International Liver Congress™
22-26 June 2022
London, United Kingdom

BACKGROUND AND AIMS

- The GLOBE score is a validated risk assessment tool providing an estimate of transplant-free survival for patients with PBC
- Seladelpar, a selective peroxisome proliferator-activated receptor (PPAR)-delta agonist, has shown potent anti-cholestatic, anti-inflammatory and anti-pruritic activity in patients with PBC
- Our aim was to evaluate change in GLOBE score in patients with PBC treated with seladelpar for 2 years
  - To examine improvement of GLOBE score and its components associated with seladelpar treatment over 2 years
  - To evaluate change in GLOBE score by age and baseline GLOBE score risk
  - To explore improvements in predicted transplant-free survival based on changes in GLOBE score observed after 2 years of treatment with seladelpar

METHODS

Baseline — 1 Year — 2 Years

Phase 2 Study Open-Label Dose Finding	Long-Term Extension Study

- Eligible patients with PBC and an inadequate response or intolerance to UDCA (alkaline phosphatase (ALP) ≥ 1.67xULN) were enrolled into an open-label one-year phase 2 study (NCT02955602) receiving daily oral 5 or 10 mg seladelpar
- After 1 year, patients were eligible for an open label long-term study (NCT03301506)
- The change in GLOBE score following seladelpar treatment over 2 years and the resulting predictions of transplant-free survival were assessed
- The contributions of alkaline phosphatase, total bilirubin, albumin, and platelets to changes in GLOBE score were examined

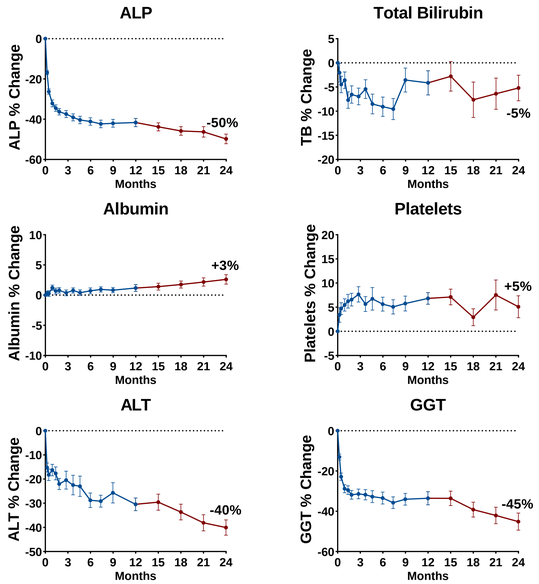
RESULTS

Demographic and Baseline Characteristics

Parameters	Total (N = 101) Mean (SD)
Female, n (%)	95 (94)
Age, years	57 (9.0)
Age at PBC Diagnosis, years	47 (8.4)
Cirrhotic, n (%)	19 (19)
AMA Positive, n (%)	91 (90)
Duration of PBC, years	10 (6.6)
Concomitant UDCA, n (%)	95 (94)
UDCA Dose, mg/kg/day	15 (3.7)
ALP (37-116 U/L)*	321 (164.9)
ALT (6-41 U/L)	49 (24.5)
AST (9-34 U/L)	44 (18.7)
GGT (7-38 U/L)	246 (170.9)
Total Bilirubin (0.1 - 1.1 mg/dL)	0.8 (0.34)
Platelet Count (140 - 400 x 10^9/L)	237 (81.7)
Albumin (3.5 - 5.5 g/dL)	4.1 (0.34)

* Normal range

Biochemical Improvement over 2 Years

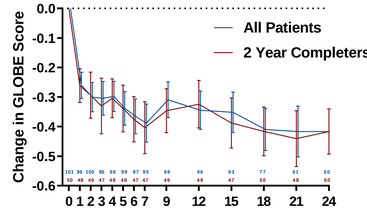


Safety

Adverse Events (AE)	Total (N = 101)
Patients with at least 1 AE	98 (97%)
Treatment-related AE	38 (37%)
Treatment-related AE ≥ Grade 3	1 (1%)
AE leading to discontinuation*	3 (3%)
SAE†	20 (20%)
Liver-related SAE	0
Treatment-related SAE	0
AE with outcome of death‡	1 (1%)
Treatment-related AE occurring > 5%	
Pruritus	8 (8%)
Nausea	7 (7%)
Diarrhea	6 (6%)
Any AE > 15%	
Pruritus	25 (25%)
Nausea	21 (21%)
Arthralgia	19 (19%)
Fatigue	19 (19%)
Urinary tract infection	18 (18%)
Diarrhea	17 (17%)

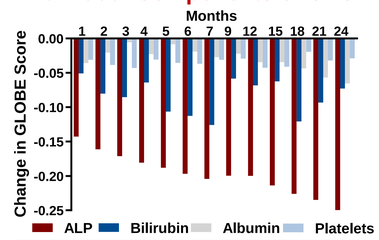
* 2 patients with grade 2 increased liver function test; 1 patient with malignant neoplasm
† 25 SAE in 20 patients (20 preferred terms)
‡ Unrelated TEAE resulting in death occurred approximately 7 months after the last dose in the seladelpar 10 mg group due to of a malignant neoplasm of unknown primary location

Change in GLOBE Score over 2 Years



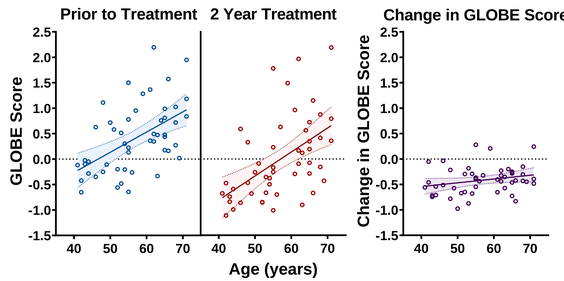
- Initial decline at Month 1 followed by additional reduction through Month 24

Change in Individual Components of GLOBE Score



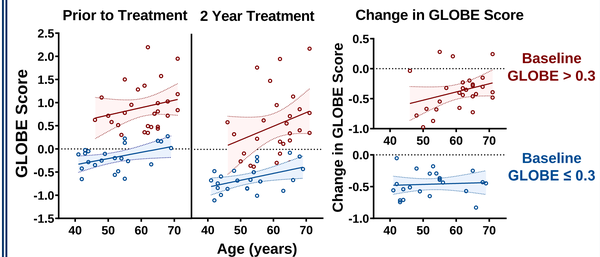
- Improvements in all components of GLOBE observed
- Greatest contributions from ALP followed by bilirubin

Change in GLOBE Score by Age after 2 Years



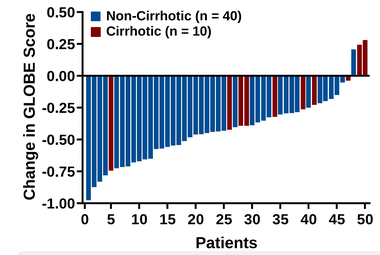
- Globe Score shifted to lower risk after 2 years treatment with no apparent dependence on age

Change in GLOBE Score by Age Group and Baseline Risk



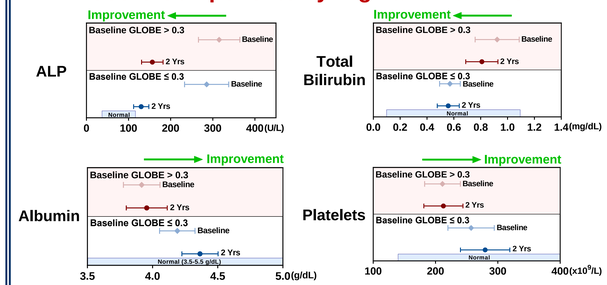
- High baseline risk: Pattern suggests that younger patients may have larger treatment effects
- Low baseline risk: Pattern suggests all ages respond similarly to treatment

Individual Patient's Change in GLOBE Score After 2 Years of Treatment



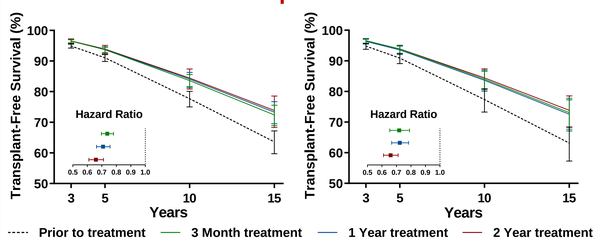
- Nearly all patients (94%) had some improvement at 2 years

Seladelpar Treatment Effects on Baseline GLOBE Score Components by High and Low Risk



- ALP effects were significant at 2 years for high and low risk
- Other components did not change significantly

Predicted Transplant-Free Survival



- Improvements in survival and hazard ratios observed as early as 3 months
- Numerically greatest improvements observed after 2 years

CONCLUSIONS

Long-term treatment of PBC patients with seladelpar

- Sustained decrease in GLOBE score led to a predicted improvement in transplant-free survival and decrease in hazard ratios
- All components of GLOBE score demonstrated improvement
  - ALP greatest followed by bilirubin
- All age groups seemed to benefit from the treatment
- Pattern by age and baseline GLOBE score risk suggested that treatment of younger patients may, irrespective of baseline risk, afford the greatest opportunity to maximize benefit and reduce risk of disease progression

Poster Discussion Online
Scan to download the poster
THE INTERNATIONAL LIVER CONGRESS™
Immune-mediated and cholestatic diseases
Bettina Hansen
DOI: 10.3252/pso.eu.ILC2022.2022
THU–461
ILC2022