Bezafibrate Add-on Therapy in High-Risk Primary Biliary Cholangitis is Associated with Prolonged Predicted Survival even in Patients with Incomplete Biochemical Improvements

Christophe Corpechot (1), Alexandra Rousseau (2), Sara Lemoinne (1), Gaouar Farid (1), Karima Ben Belkacem (1), Raoul Poupon (1), Olivier Chazouillères (1)

(1) Reference Center for Inflammatory Biliary Diseases and Autoimmune Hepatitis (MIVB-H), Inserm UMR_S938, Saint-Antoine Hospital and Research Center (CRSA), Assistance Publique – Hôpitaux de Paris (APHP), Sorbonne University, Paris; (2) Clinical Research Platform of East of Paris, Saint-Antoine Hospital, APHP, Paris, France

1 INTRODUCTION

- Data from the BEZURSO trial [1] showed that bezafibrate (BZF) therapy in addition to continued ursodeoxycholic acid (UDCA) increased the rate of complete biochemical response in patients with high-risk primary biliary cholangitis (PBC).
- However, not all patients from this trial equally responded to BZF add-on and the efficacy of this treatment in incomplete responders remains uncertain.

2 AIM

This post-hoc analysis of the BEZURSO trial aimed to characterize the factors predictive of, and the predicted outcomes associated with, an incomplete response to BZF add-on therapy in high-risk PBC patients.

3 METHOD

- The study population included 100 patients with a Paris-2 incomplete response to UDCA who were randomly assigned to BZF 400 mg/d (n=50) or placebo (n=50), in addition to continued UDCA therapy, for 24 months.
- Incomplete response to BZF was defined at the end of study (EOS) based on either the Paris-2 criteria or the absence of complete biochemical response (primary outcome).
- The predictive factors of incomplete response to BZF add-on therapy were studied using a logistic regression model.
- The Globe and UK-PBC risk scores [2, 3] were used to estimate the predicted mortality or need for liver transplantation (LT) in complete and incomplete responders from each treatment group.
- The Dwass-Steel-Critchlow-Fligner and Kruskal-Wallis tests were used for the comparison of groups.

4 RESULTS

- Among the 50 patients of the BZF group, a total of 14 (30%) out of 46 patients with available biochemical data at 24 mo. still exhibited a Paris-2 incomplete response to BZF add-on therapy at EOS.
- In a univariate analysis, clinically significant pruritus (itch score ≥ 3), portal hypertension (PH), high values of liver stiffness as assessed by vibration-controlled transient elastography (Fibroscan), and high serum levels of total bilirubin, ALP, or AST were baseline factors associated with Paris-2 incomplete biochemical response to BZF add-on therapy (**Table 1**).
- In a multivariable analysis, PH and high levels of ALP (optimal high risk threshold > 2.53 xULN) were independent predictors of incomplete biochemical response to BZF add-on therapy (**Table 2**).
- The relative changes from baseline to EOS in ALP levels of BZF complete responders (BCR), BZF incomplete responders (BIR), and placebo patients (PP) are shown in **Figure 1**.
- The EOS ALP levels in BCR, BIR, and PP are shown in **Figure 2**.
- The median (interquartile) relative changes from baseline to EOS in 15-year Globe and UK-PBC predicted mortality or need for LT of BCR, BIR, and PP are shown in **Figure 3**.
- They were -45% (-58%; -25%), -16% (-41%; -3%), and 14% (-1%; 47%), respectively as estimated by the Globe score and -43% (-61%; -16%), -13% (-32%; 13%), and 22% (7%; 50%), respectively as estimated by the UK-PBC score (p<0.001 for both models).
- The predicted mortality or need for LT in BIR was significantly reduced as compared to PP (p<0.01 and p<0.05 for Globe and UK-PBC models, respectively; **Figure 3**).

Table 1. Univariate analysis

	Odds ratio [95%CI]
Portal hypertension	12.89 [1.27 - 130.55]
Itch score ≥ 3	5.83 [1.36 - 24.94]
AST – x ULN	3.96 [1.29 - 2.93]
ALP – x ULN	3.90 [1.25 - 12.22]
Bilirubin – µmole/L	1.17 [1.04 - 1.33]
Liver stiffness – kPa	1.14 [1.00 - 1.29]

Table 2. Multivariable analysis

	Odds ratio [95%CI]
Portal hypertension	15.20 [1.22 - 189.56]
Itch score ≥ 3	-
AST – x ULN	-
ALP – x ULN	4.28 [1.21 - 15.08]
Bilirubin – µmole/L	-
Liver stiffness – kPa	-

Figure 1. Relative changes from baseline to EOS in serum ALP level (median, IQR)

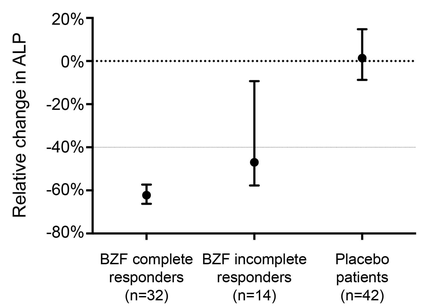


Figure 2. Serum ALP levels at EOS (median, interquartile)

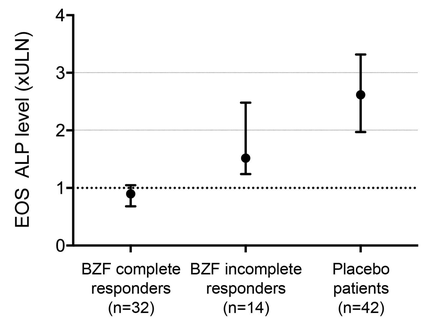
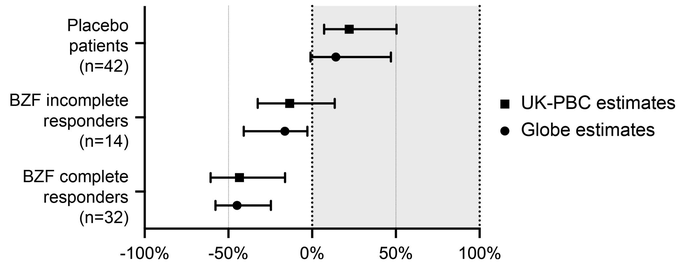


Figure 3. Relative changes from baseline to EOS in 15-year predicted mortality or need for liver transplantation (median, interquartile)



5 CONCLUSIONS

- A third of PBC patients with an incomplete UDCA Paris-2 response at baseline still exhibits an incomplete biochemical response after 24 months of BZF add-on therapy.
- At baseline, these patients more frequently show features of portal hypertension or ALP levels > 2.53 xULN.
- At 24 months, their ALP levels and predicted mortality or need for LT are significantly lower than those of UDCA plus placebo-treated patients, suggesting that BZF add-on therapy should not be discontinued in this situation.

6 ACKNOWLEDGEMENTS

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7 REFERENCES

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8 CONTACT

christophe.corpechot@aphp.fr

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