Changes in serum bile acid levels associated with bezafibrate add-on therapy in patients with primary biliary cholangitis and inadequate biochemical response to ursodeoxycholic acid: results from the BEZURSO trial (NCT01654731)

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INTRODUCTION

We recently reported the results of a 24-month, multicenter, double-blind, randomized, placebo-controlled trial of bezafibrate (BZF) add-on therapy in patients with primary biliary cholangitis (PBC) and inadequate biochemical response to ursodeoxycholic acid (UDCA).[1] (Figure 1)

These results showed that a combination of BZF with UDCA is associated with a significant improvement in the symptoms, standard biochemical liver tests, and prognostic markers of the disease. Here, we assessed the changes in serum bile acid (BA) profiles and C4 precursor levels associated with these therapeutic effects.

AIM

To study the effects of Bezafibrate add-on therapy on BA synthesis and serum profiles of patients with PBC who had previously failed to respond to UDCA.

MATERIAL & METHODS

Fasting serum levels of BA and C4 precursor (a marker of BA synthesis) were assessed from serum samples collected at baseline (M0), month-12 (M12), and month-24 (M24, end of trial) of the BEZURSO trial in both the BZF and placebo (PLB) groups.

The concentrations of total, primary and secondary (i.e. endogenous) BA, UDCA, and C4 precursor were determined using a high-performance liquid chromatography-mass spectrometry method.

Concentrations, percentages, and relative changes in BA species were compared between the BZF and placebo groups, and according to the biochemical response to BZF using nonparametric tests. Analyses were performed on the intent-to-treat population.

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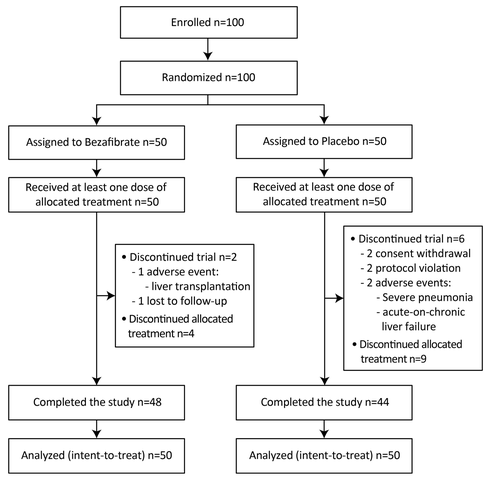
Figure 1. Flowchart of the BEZURSO trial



Of the 100 patients participating in the trial, M0, M12, and M24 serum samples were available in 91, 82, and 79, respectively. Eighty-one patients had at least 2 consecutive samples including M0. At baseline, both the BZF (n=45) and PLB (n=46) groups were similar for total and individual BA concentrations and C4 precursor levels (Table 1).

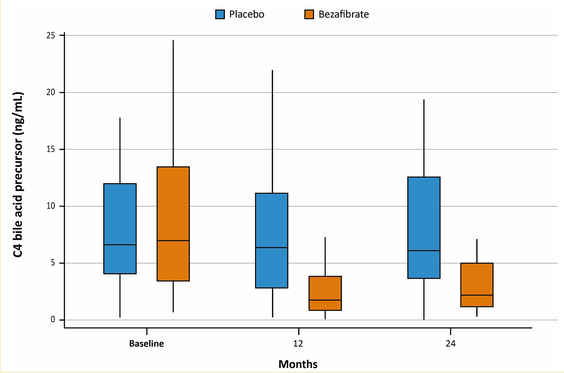
Table 1. Serum levels of bile acids and C4 precursor at baseline according to trial group

	Placebo	Bezafibrate
Total BA - µmole/L	37.4 ± 44.8	40.7 ± 39.9
CA - µmole/L	5.0 ± 6.1	4.8 ± 6.9
CDCA - µmole/L	4.4 ± 5.1	5.4 ± 7.5
DCA - µmole/L	2.0 ± 2.3	2.1 ± 2.3
LCA - µmole/L	0.3 ± 0.3	0.3 ± 0.3
UDCA - µmole/L	25.6 ± 37.7	28.1 ± 26.2
C4 precursor – ng/mL	8.4 ± 8.1	9.3 ± 8.4

RESULTS

Changes in C4 precursor were significantly different between groups, with a 70% reduction in the BZF group and no modification in the placebo group (p=0.0011, Figure 2).

Figure 2. Changes from baseline in serum level of C4 bile acid precursor according to trial group



The overall changes in total BA at M24 did not differ significantly between the 2 groups despite a trend towards a reduction in cholic acid concentration (Table 2).

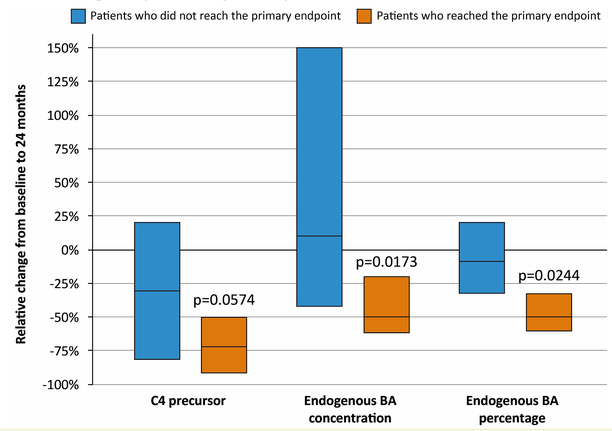
Table 2. Relative changes from baseline to 24 months in BA concentrations according to trial group

	Placebo	Bezafibrate	P-value
Total BA	0.1 (- 0.2 – 2.0)	0.1 (- 0.2 – 1.3)	0.6584
CA	0.2 (- 0.4 – 1.7)	- 0.4 (- 0.7 – 0.7)	0.0526
CDCA	0.0 (- 0.3 – 2.3)	0.2 (- 0.4 – 1.3)	0.5892
DCA	- 0.3 (- 0.6 – 0.3)	- 0.6 (- 0.8 – 0.5)	0.2371
LCA	- 0.1 (- 0.7 – 0.5)	- 0.3 (- 0.7 – 0.4)	0.8859
UDCA	0.3 (- 0.3 – 3.4)	0.2 (- 0.2 – 1.4)	0.5492

However, the percentage of endogenous BA was significantly reduced in the BZF compared to the PLB group both at M12 (21% *vs*. 29%; p=0.009) and M24 (18% *vs*. 25%; p=0.0260).

Furthermore, reductions from baseline to M24 in both endogenous BA concentration and percentage and in C4 precursor were significantly higher in the patients who reached the primary endpoint of the trial (i.e. normal total bilirubin, alkaline phosphatases, transaminases, albumin and prothrombin time), as opposed to the others (Figure 3).

Figure 3. Relative changes in C4 and endogenous BA according to primary endpoint



CONCLUSION

Bezafibrate add-on therapy in patients with PBC and inadequate response to UDCA is associated with a marked decrease in serum level of C4 precursor.

The beneficial effect of BZF on biochemical liver tests is associated with a parallel decrease in serum level of C4 precursor and endogenous BA concentration and percentage, suggesting it is, at least in part, mediated by a reduction in BA synthesis and hepatocellular overload.

REFERENCES

[1] Corpechot et al. J Hepatol 2017, vol. 66, issue 1, S89

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