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Improved markers of cholestatic liver injury in patients with primary biliary cholangitis treated with obeticholic acid and bezafibrate

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Abbreviations

PBC

Primary biliary cholangitis

ALP

Alkaline phosphatase level

UDCA

Ursodeoxycholic acid

OCA

Obeticholic acid

POISE

PBC OCA International Study of Efficacy

VAS

Visual analogue scale

A decrease or normalization of alkaline phosphatase (ALP) and bilirubin levels in patients treated for primary biliary cholangitis (PBC) predicts a better survival (1). Obeticholic acid (OCA) is the approved second-line therapy if ursodeoxycholic acid (UCDA) fails, but its use may worsen pruritus (2). Adding bezafibrate to UCDA improved biochemical markers of cholestatic liver injury and decreased pruritus severity (3,4). Because normalization of ALP and bilirubin was only achieved in a minority of patients in these studies, we explored whether bezafibrate (off-label drug) could improve the effect of OCA (licensed drug) on cholestasis.

Methods

Thirteen patients who had participated in the POISE trial (2) and still had ALP levels exceeding the normal range despite UDCA (13-15 mg/kg/day) and OCA (5-10 mg/day) therapy, were considered for inclusion in this prospective clinical case series trial. Add-on bezafibrate treatment (Eulitop, 400 mg/day) was prescribed for 1 year (triple therapy) after statins were stopped. Next, over a period of 6 months OCA was withdrawn, independent of whether the patient achieved ALP normalization during triple therapy. The OCA dose was gradually reduced until an increase in ALP occurred. OCA was then re-introduced in the same dosage as the one at baseline. In patients without increased ALP, OCA was stopped completely. The trial design is shown in supplementary Figure 1. Pruritus was assessed every 3 months with the pruritus subcategory of the PBC-40 questionnaire and the VAS (visual analogue scale) score. Mild pruritus was defined as a VAS score <4 and moderate pruritus as ≥ 4 and <7. Continuous variables were expressed by the mean (SD). A paired t-test p-value of <5% was considered statistically significant.

Results

Of the 13 patients considered for this trial, 1 patient was excluded because of HCC and 1 was reluctant to participate. Eleven patients started the triple therapy. Laboratory parameters are shown in Table 1. Three patients developed myalgia within 2 weeks after the start of triple therapy, leading to bezafibrate discontinuation in 1 patient and a dose reduction to 400 mg/2 days in 2 others. There was no rhabdomyolysis.

After 1 year of triple therapy, a significant decrease in ALP ($p < 0.001$) was observed: ALP decreased in 9/10 patients (Figure 1A) and normalized in 7/10. There was a significant decrease ($p < 0.01$) in bilirubin: 8/10 patients had bilirubin levels $\leq 0.6 \times$ ULN (Figure 1B). One patient presented with a grade 1 ALT elevation. A tendency towards increased creatinine levels was observed, but none of the patients presented with a grade 1 elevation. No significant changes in other laboratory parameters were observed (Table 1). Using the PBC-40 questionnaire, 8/11

patients reported pruritus at the start and after 1 year triple therapy, 6/10 reported pruritus. Using the VAS score, 7/11 reported pruritus at the start (3 mild and 4 moderate) with a mean score of 2.3 points. After 1 year, 5 patients reported no pruritus, 4 mild and 1 moderate. The mean VAS score decreased to 1.3 points (ns).

The OCA withdrawal phase was started in 10 patients and OCA re-introduction was needed in 5/10. In the latter, mean ALP increased from 138 U/L at baseline to 257 U/L under withdrawal. Among the 5 patients who required re-introduction, 3 did not achieve normal ALP after 1 year of triple therapy.

Discussion

OCA and bezafibrate are second-line therapies for PBC, but normalization of ALP and bilirubin only occurs in a limited number of patients. We here show that triple therapy of UDCA, OCA and bezafibrate further improved and even normalized markers of cholestasis in the majority of patients with PBC who failed to respond to UDCA and OCA therapy. An industry-driven phase-2 study was recently initiated to confirm these data and further address efficacy and safety.

References

1. Murillo Perez CF, Harms MH, Lindor KD, van Buuren HR, Hirschfield GM, Corpechot C, et al. Goals of Treatment for Improved Survival in Primary Biliary Cholangitis. *Am J Gastroenterol* 2020;115:1066–1074.
2. Nevens F, Andreone P, Mazzella G, Strasser SI, Bowlus C, Invernizzi P, et al. A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis. *N Engl J Med* 2016;375:631–643.
3. Corpechot C, Chazouillères O, Rousseau A, Le Gruyer A, Habersetzer F, Mathurin P, et al. A Placebo-Controlled Trial of Bezafibrate in Primary Biliary Cholangitis. *N Engl J Med* 2018;378:2171–2181.
4. Reig A, Sesé P, Parés A. Effects of Bezafibrate on Outcome and Pruritus in Primary Biliary Cholangitis With Suboptimal Ursodeoxycholic Acid Response. *Am J Gastroenterol* 2018;113:49–55.

Figure Legend

Figure 1

(A) Changes in mean (SD) ALP levels. Normal range for male (≤ 130 U/L) and female (≤ 105 U/L). **(B)** Changes in mean (SD) bilirubin levels. Normal range $<20,18 \mu\text{MOL/L}$.

** $p < 0.01$; *** $p < 0.001$.

Abbreviation: Beza, bezafibrate.

Other Manuscript Elements

Author Contribution (CRediT taxonomy)

Lena Smets	Writing – original draft
Jef Verbeek	Writing – review & editing
Hannelie Korf	Writing – review & editing
Schalk van der Merwe	Writing – review & editing
Frederik Nevens	Supervision

Conflict of Interest

Prof. dr. Frederik Nevens received fee for advisory boards and speakers' bureau from Intercept Pharmaceuticals.

Parameter Mean ± SD	Baseline DUAL therapy (n=11)	1 year DUAL therapy (n=11)	Baseline TRIPLE therapy (n=11)	1 year TRIPLE therapy (n=10)	p-values
ALP (U/L)	324 ± 68	207 ± 37	201 ± 56	112 ± 42	0.0005
Bilirubin (μMOL/L)	12.4 ± 9.6	9.6 ± 3.8	11.6 ± 8.6	8.7 ± 7.7	0.0026
ALT (U/L)	50 ± 29	27 ± 18	25 ± 10	28 ± 10	0.1589
AST (U/L)	49 ± 28	37 ± 22	36 ± 15	40 ± 16	0.0862
GGT (U/L)	300 ± 243	96 ± 97	100 ± 137	64 ± 57	0.2352
Creatinine (μMOL/L)	64.3 ± 9.0	62.2 ± 9.0	78.1 ± 17.2	81.5 ± 13.4	0.9172
Triglycerides (mg/dL)	110 ± 28	92 ± 23	103 ± 25	119 ± 43	0.1489
Cholesterol (mMOL/L)	7.0 ± 3.5	5.1 ± 0.8	4.9 ± 0.8	4.6 ± 0.6	0.2526
HDL (mg/dL)	75 ± 25	63 ± 20	64 ± 16 (n=7)	60 ± 13 (n=7)	0.2501
LDL (mg/dL)	135 ± 29	119 ± 29	123 ± 17 (n=7)	97 ± 19 (n=7)	0.0827
IgM (g/L)	5.4 ± 4.5	n.a.	2.8 ± 2.0	2.5 ± 2.4	0.3209
Fibroscan (kPa)	11.2 ± 7.6	10.1 ± 7.7	13.5 ± 13.4	11.4 ± 14.9	0.3539

Table 1.

Characteristics of patients who entered the triple therapy phase.

Biochemical parameters at baseline and after 1 year of dual therapy (UDCA and OCA: POISE) and at baseline and after 1 year of triple therapy (UDCA, OCA and bezafibrate). p-values were calculated between baseline triple therapy and one year triple therapy.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; n.a., not available

A

B

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