Response failure to ursodeoxycholic acid treatment in primary biliary cholangitis is associated with a distinct stool and urine secondary bile acid profile

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Introduction

Primary biliary cholangitis (PBC) is an autoimmune cholestatic liver disease that can lead to progressive liver damage. The first-line treatment for PBC is ursodeoxycholic acid (UDCA); a hydrophilic bile acid which delays disease progression and improves biochemical markers of liver damage such as serum alkaline phosphatase (ALP). Patients who do not respond to UDCA have persistently altered serum biochemistry which is associated with higher risk of liver transplant and lower survival. Mechanisms underlying treatment failure remain unknown.

Aim

We profiled patient bile acids (BAs) to investigate whether differing UDCA treatment responses relate to changes in BA metabolism.

Methods

Serum, urine and faeces of 454 patients in the UK-PBC cohort treated with UDCA for at least 1 year were collected and BA profiled with Ultra-High Performance Liquid Chromatography coupled to Mass Spectrometry (UHPLC-MS). Linear mixed effects models were fitted to each BA feature to assess differences across treatment responses, while adjusting for age, gender, body mass index, alcohol consumption, smoking, antibiotics and proton pump inhibitors as fixed effects, and patient recruitment site as random effect. Likelihood ratio test was used to assess significance, p values adjusted using the Benjamini-Hochberg method and null hypothesis rejected with adjusted p value < 0.1.

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Results

We defined 3 response groups: responders with good prognosis (R_GP; n= 224), with a > 40% reduction or normalised ALP levels after 1 year of treatment, responders with bad prognosis (R_BP; n= 16), with reduced ALP still higher than 1.67 times the upper limit of normal, and non-responders (NR; n= 214), who failed to reduce ALP. 12 stool and 8 urine BA were differently abundant, while there were no differences in serum. Stool BA displayed opposite trends in R_BP and R_GP with respect to non-responders (Figure); faecal UDCA increased in R_GP (95% CI [0.05, 0.23]) but not in R_BP (95% CI [-0.2, 0.25]). Urine BA decreased in R_GP, except for 12-dehydrocholic acid (95% CI [0.06, 0.36]). In addition, the total pool of glycated BAs in R_GP was higher in stool (95% CI [0.04, 0.17]), and lower in urine (95% CI [-0.19, -0.55]) compared to NR.

Figure 1. Response to UDCA treatment varies across patients

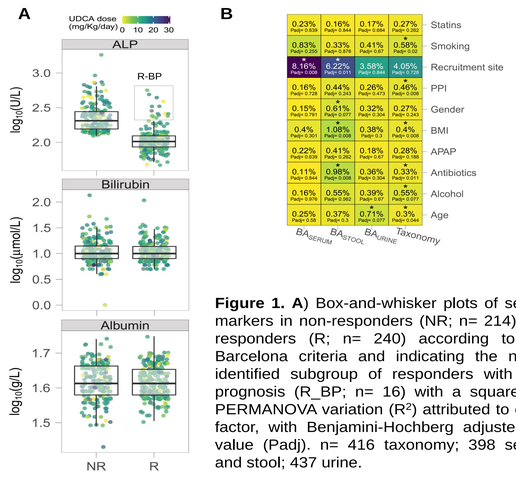


Figure 1. **A**) Box-and-whisker plots of serum markers in non-responders (NR; n= 214) and responders (R; n= 240) according to the Barcelona criteria and indicating the newly identified subgroup of responders with bad prognosis (R_BP; n= 16) with a square. **B**) PERMANOVA variation (R^2) attributed to each factor, with Benjamini-Hochberg adjusted P-value (Padj). n= 416 taxonomy; 398 serum and stool; 437 urine.

Figure 2. Bile acids in faeces and urine differ with UDCA response

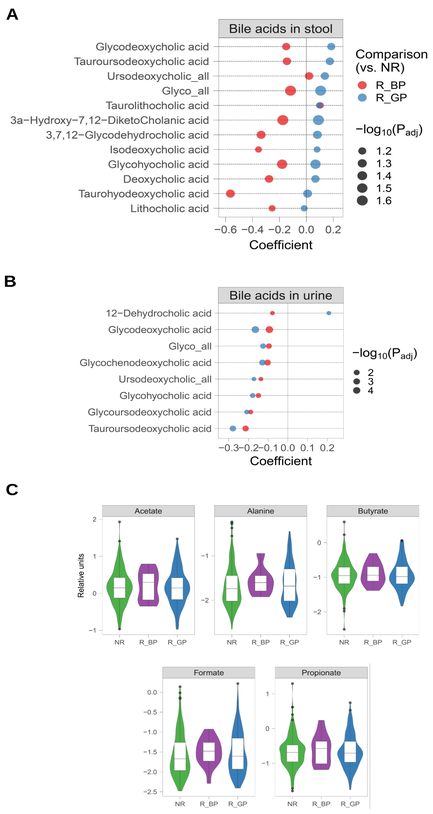
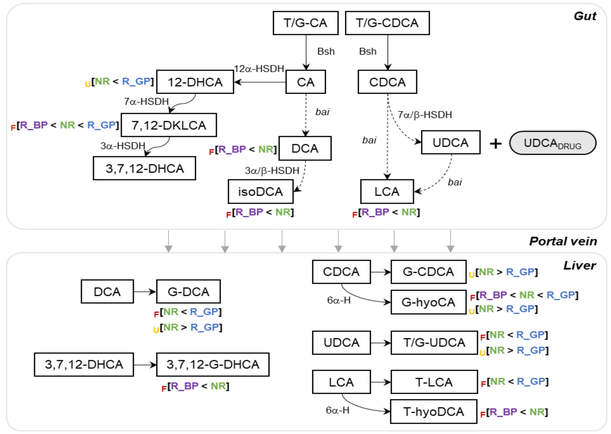


Figure 2. Regression coefficients of bile acids significantly different (Benjamini-Hochberg Padj < 0.1) in stool (**A**) and urine (**B**), with non-responders as reference category, and levels of annotated stool short-chain fatty acids according to UDCA response (**C**). n= 398 stool (186 NR; 197 R_GP; 15 R_BP); n=437 urine (207 NR; 214 R_GP; 16 R_BP).

Figure 3. Treatment response changes and proposed metabolic alterations



	Deconjugation	Oxo-epimerisation	7α-dehydroxylation	Re-conjugation Detoxification
NR		↓		↓
R_GP		↑		↑
R_BP	↓			

microbial — host

Figure 3. R_GP had higher faecal excretion of conjugated secondary and oxo-BAs and increased urine 12-dehydrocholate. R_BP had lower excretion of unconjugated secondary BAs. Dashed arrows indicate multi-step reactions. Summary table blank cells indicate that our data do not provide enough evidence of whether these pathways are different across groups. U: urine; F: faeces; T/G: tauro-/glyco-conjugated; CA: cholic acid; CDCA: chenodeoxycholic acid; DCA: deoxycholic acid; UDCA: ursodeoxycholic acid; LCA: lithocholic acid; DHCA: dehydrocholic acid; DKLCA: diketolithocholic acid; Bsh: bile salt hydrolase; bai: BA-induced operon enzymes for 7α-dehydroxylation; HSDH: hydroxysteroid dehydrogenase; 6α-H: 6-α hydroxylase (CYP3A4).

Conclusions

Response to UDCA treatment is associated with a different bile acid signature in PBC, mainly involving microbial-derived secondary BA. These findings suggest a contribution of the intestinal microbiota to the response phenotype.

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