Odevixibat Treatment Induces Biliary Bile Acid Secretion in Responsive Patients With Bile Salt Export Pump Deficiency

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Progressive familial intrahepatic cholestasis (PFIC) refers to a heterogeneous group of rare liver diseases consisting of genetically defined subtypes all characterized by defective bile formation and pruritus.[1] Deficiency of the bile salt export pump (encoded by the *ABCB11* gene), referred to as PFIC type 2 (PFIC2), leads to defective hepatobiliary transport of bile acids (BAs), resulting in hepatic BA accumulation and cholestatic liver damage.[2]

Odevixibat, an inhibitor of the ileal BA transporter (IBAT, also known as apical sodium-BA transporter), blocks reabsorption of conjugated BAs from the terminal ileum and hence promotes their passage into the colon and subsequent excretion into feces.[3,4] In a randomized, placebo-controlled study, odevixibat reduced the concentration of serum BAs (sBA) in patients with different types of PFIC, including PFIC2[3] (PEDFIC1 study, NCT03566238). PFIC2 patients receiving odevixibat could be divided into responders (Rs) and nonresponders (NRs). Responsiveness was defined per protocol as a reduction of sBA concentration by more than 70% or reaching a total sBA concentration below 70 μmol/L at the end of treatment at 22–24 weeks. To further characterize odevixibat Rs vs NRs in bile salt export pump deficiency, we analyzed the sBA composition at the end of treatment of all 45 genetically confirmed PFIC2 patients who participated in PEDFIC1, divided into 15 Rs (8 women), 15 NRs (10 women) and 15 (7 women) patients receiving placebo.

We quantified the absolute concentrations of individual BA species using liquid chromatography–tandem mass spectrometry and calculated the relative concentrations of unconjugated BAs; the primary BAs cholic acid (CA) and chenodeoxycholic acid (CDCA); the secondary BAs deoxycholic acid, ursodeoxycholic acid, and lithocholic acid; and the ratio of glycine-to taurine conjugated (G/T ratio) BAs. Ursodeoxycholic acid was used in the treatment of several patients participating in PEDFIC1. We therefore subtracted ursodeoxycholic acid concentration from the total sBA concentration after which the percentage of contribution of each of the BAs to the total sBA concentration was calculated. Data were not normally distributed, and a Mann-Whitney U test was used to assess differences between separate groups. The median value (range) is reported for each group.

Conjugated BAs that escape IBAT reabsorption reach the colon, where they can be deconjugated by bacteria with bile salt hydrolase activity to form unconjugated BAs.[5] The median contribution of unconjugated sBA to total sBA was more than 70-fold higher in Rs (3.7%; range, 0.06%–28.4%) compared with NRs (0.05%; range, 0.03%–0.3%; $P < .001$) and placebo (0.05%; range, 0.02%–1.24%; $P < .001$) (Figure 1*A*). Both unconjugated CA and unconjugated CDCA contributed to this difference (data not shown). The absolute concentration of unconjugated sBA was 2-fold higher in Rs (0.2 μmol/L; range, 0.08–0.8) compared with NRs (0.1 μmol/L; range, 0.08–0.3; $P = .02$) and placebo (0.1 μmol/L; range, 0.06–0.2; $P = 0.002$) (Supplementary Table 1). Median secondary BA fractions were very low and did not differ between the groups (Figure 1*B*). The median G/T conjugation ratio was higher in Rs (6.0; range, 2.0–12.7) than in NRs (2.9; range, 1.6–4.3; $P < .001$) and placebo (3.0; range, 1.3–4.5; $P < .001$) and reached values comparable with those reported from healthy children.[6,7] The median CA/CDCA ratio was lower in Rs (0.6; range, 0.3–3.1) compared with NRs (1.8; range, 0.9–3.9; $P = .002$) and placebo (2.5; range, 1.0–5.2; $P < .001$) (Figure 1*C* and *D*). The CA/CDCA ratio in Rs was comparable with that reported from healthy children.[6,7]

These results provide 3 important new insights in the mechanism of the apparent anticholestatic actions of odevixibat in responding PFIC2 patients. First, in responsive patients, the observed high fraction and high absolute concentration of unconjugated sBA results from improved hepatobiliary BA secretion. The relative and absolute increase in unconjugated BAs in serum indicates the appearance of BAs into the peripheral circulation that must be of intestinal origin. The virtual absence of unconjugated BAs in serum of placebo and NRs and their presence in Rs may suggest that inhibition of conjugated BA reabsorption by odevixibat effectively induces hepatobiliary BA secretion. This hepatobiliary BA secretion may be responsible for the reduction of the total sBA concentration in Rs; however, this remains speculative.

Second, responsiveness to odevixibat does not (at least not after 22–24 weeks of treatment) coincide with a reappearance of secondary BAs, which are formed by bacterial dehydroxylation *after* deconjugation of primary BAs and were only present in minimal amounts in some patients. The lack of secondary BA formation in the colon of responsive patients may be due to an absence of bacteria with BA dehydroxylating activity or due to a rapid colonic transit. Detailed characterization of fecal BA composition and microbiome composition in future studies is expected to provide more insight, but stool samples have not been collected in the PEDFIC1 study.

Third, responsiveness to odevixibat was associated with an increase of the G/T ratio and a decrease of the CA/CDCA ratio in sBA, which may both reflect normalization of BA

Abbreviations used in this paper: **BA, bile acid; CA, cholic acid; CDCA, chenodeoxycholic acid; G/T ratio, glycine-to-taurine conjugation ratio; IBAT, ileal bile acid transporter; NR, nonresponder; PFIC, progressive familial intrahepatic cholestasis; PFIC2, progressive familial intrahepatic cholestasis type 2; R, responder; sBA, serum bile acid.**

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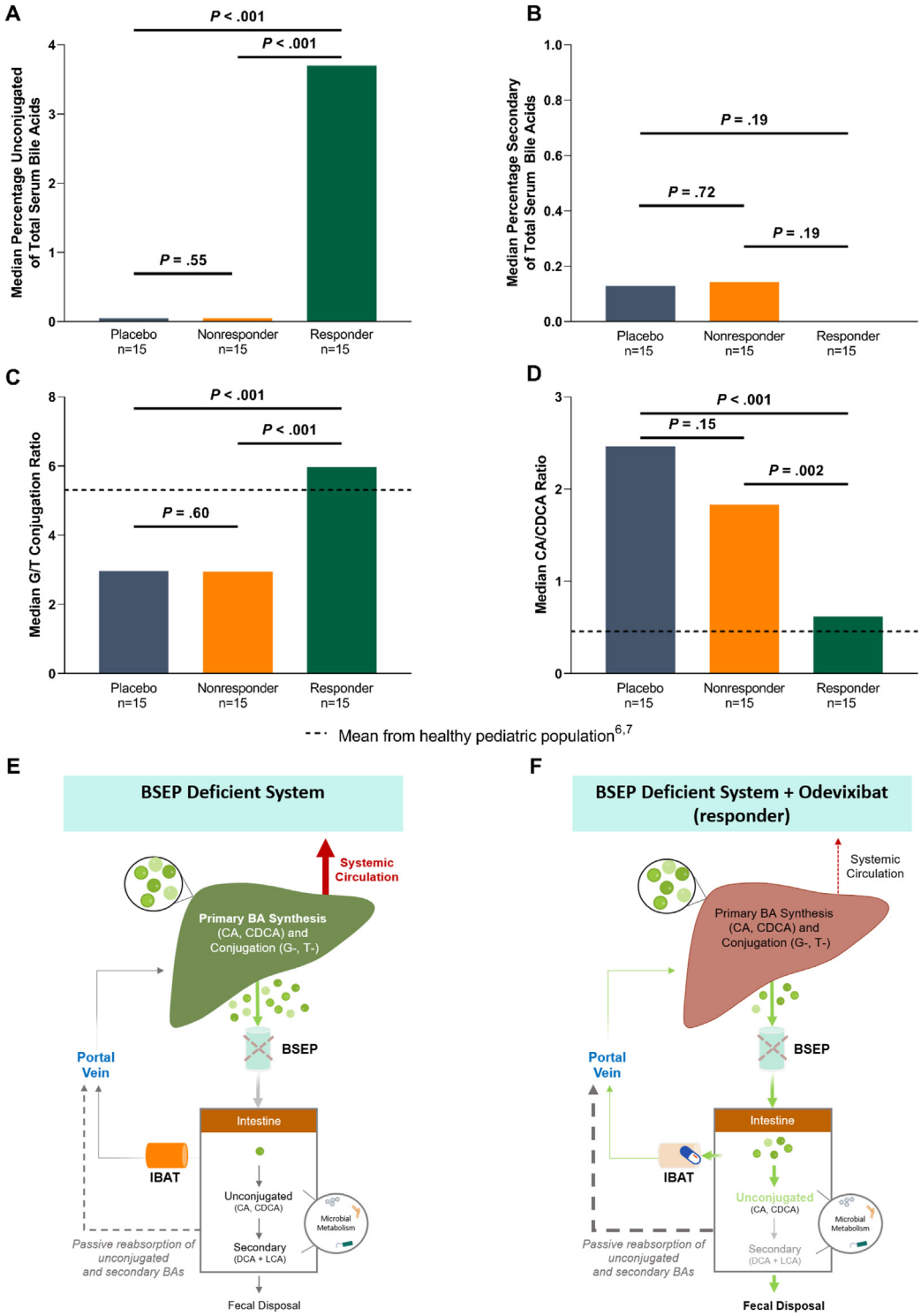

Figure 1. The median percentage that unconjugated (*A*) and secondary (*B*) sBA contribute to the total sBA concentration in PFIC2 patients of the PEDFIC1 study in the R, NR, and placebo patient groups. Median G/T ratio (*C*) and CA/CDCA ratio (*D*) in the R, NR, and placebo patient groups. (*E*) Schematic overview of patients with bile salt export pump (BSEP) deficiency at baseline showing impaired secretion via BSEP with resulting low intestinal BAs but effective reabsorption via IBAT and passive diffusion. (*F*) Schematic overview of patients with BSEP deficiency who are responsive to IBAT inhibition. Reabsorption via IBAT is inhibited, resulting in increased excretion of BAs leading to a decrease in total sBA. There is relatively more reabsorption by passive diffusion compared with *E*.

homeostasis based on comparison with healthy children.[6,7] A *decreased* G/T ratio has been described in biliary atresia patients with persistent cholestasis after Kasai portoenterostomy and may therefore be an indication of liver injury. The CA/CDCA ratio at the end of treatment in odevixibat-responsive PFIC2 patients was not only similar to that in healthy children but also to that in biliary atresia patients with a good prognosis on survival after Kasai portoenterostomy.[8]

The altered G/T ratio and CA/CDCA ratio may be due to preferential passive reabsorption of specific BA species from the intestine. Although the contribution of non-IBAT–mediated reabsorption is usually minor, glycine conjugates and CDCA are more hydrophobic and are more readily reabsorbed by passive means as compared with taurine conjugates and CA, respectively.[9] This difference in passive reabsorption may have more influence on sBA composition when IBAT is inhibited. Assessment of biliary and fecal BA composition in follow-up studies will provide more insight. Interindividual differences in the fraction of unconjugated sBA, G/T ratio, and CA/CDCA ratio within R, NR, and placebo subgroups (Supplementary Figure 1) may originate from interindividual variation in the ratio in which primary BAs are synthesized, cycling time of the enterohepatic circulation, and metabolic conversion capacity of the colonic microbiome.[5]

In conclusion, odevixibat, a nonabsorbable, intestinally active IBAT inhibitor, may induce hepatobiliary BA secretion in responsive PFIC2 patients as illustrated by a high unconjugated sBA fraction and may lead to improved prognostic serum BA parameters of liver health (Figure 1*E* and *F*). Normalization of G/T conjugation ratios and CA/CDCA ratios may indicate recovery of a healthy hepatic BA production after 24 weeks of treatment with odevixibat in responding PFIC2 patients.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org and at https://doi.org/10.1053/j.gastro.2023.03.226.

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Conflicts of interest
These authors disclose the following: Folkert Kuipers has had consultant fees paid to the University of Groningen from Albireo. Erik Lindström and Velichka Valcheva are employees of Albireo. Henkjan J. Verkade has received grants paid to the University of Groningen from Albireo and Mirum and consultant fees paid to the University of Groningen from Ausnutria BV, Albireo, Danone/Nutricia Research, Intercept, Mirum, Orphalan, and Vivet. The remaining authors disclose no conflicts.

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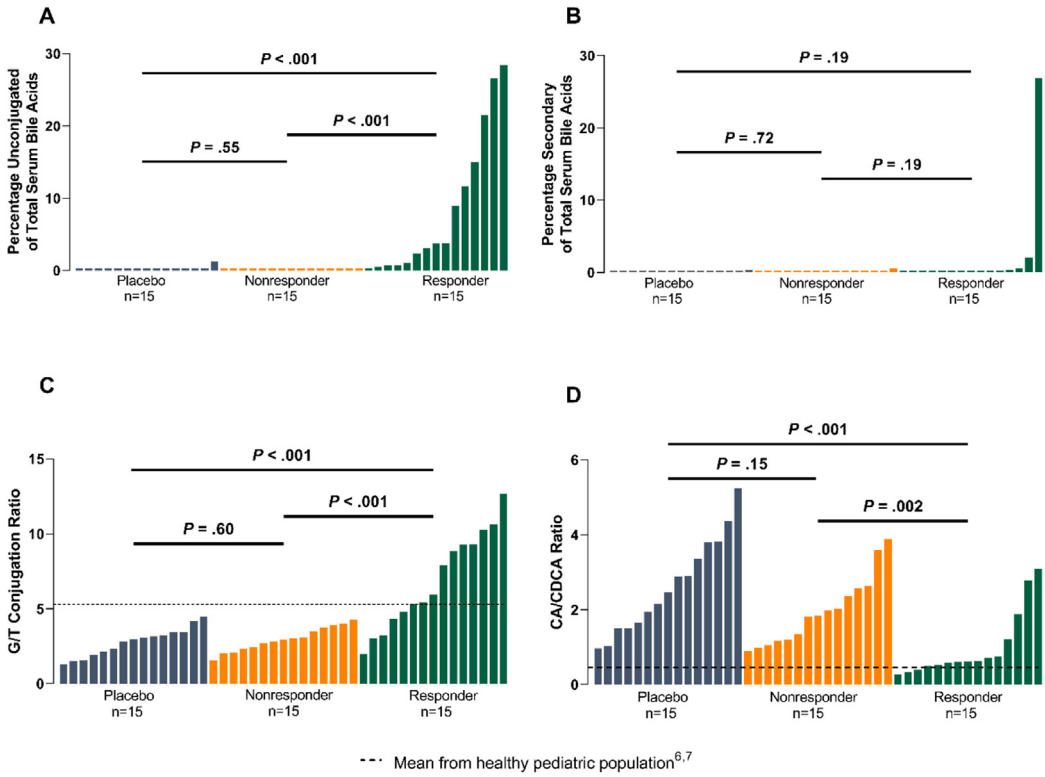

Supplementary Figure 1. The percentage that unconjugated (*A*) and secondary (*B*) sBA contribute to the total sBA concentration in each individual PFIC2 patient of the PEDFIC1 study, grouped by response category or placebo. G/T ratio (*C*) and CA/CDCA ratio (*D*) per individual patient, grouped by response category or placebo, with *horizontal dashed line* indicating mean values reported from healthy children.

Supplementary Table 1. Median Absolute Concentration of Total Unconjugated, Total Secondary sBA, Unconjugated CA, and Unconjugated CDCA in PFIC2 Patients of the PEDFIC1 Study in the R, NR, and Placebo Patient Groups

	sBA Concentration (μmol/L)			*P* value		
	Placebo (n = 15)	NR (n = 15)	R (n = 15)	P vs NR	P vs R	NR vs R
Total unconjugated	0.10 (0.06–0.16)	0.11 (0.08–0.31)	0.20 (0.08–0.82)	.31	.002	.02
Unconjugated CA	0.05 (0.03–0.10)	0.05 (0.03–0.15)	0.06 (0.03–0.43)	.65	.11	.32
Unconjugated CDCA	0.05 (0.03–0.10)	0.05 (0.03–0.15)	0.10 (0.05–0.40)	.18	<.001	.02
Total secondary	0.28 (0.03–0.58)	0.27 (0.15–1.49)	0.00 (0.00–2.26)	.76	<.001	<.001

Values are median (range).