Differential expression of bile acid subspecies with maralixibat treatment in pruritus responders with bile salt export pump deficiency

Xueheng Zhao,[1] Pamela Vig,[2] Andrew J Wardle,[2] Kenneth D R Setchell[3]

[1]Division of Pathology and Laboratory Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [2]Mirum Pharmaceuticals, Foster City, CA, USA; [3]College of Medicine, University of Cincinnati, Cincinnati, OH, USA

FRI-296

Introduction

- Progressive familial intrahepatic cholestasis (PFIC) is a genetic disease resulting in the absence of, or reduction in, bile salt export pump (BSEP) activity.[1] It causes severe cholestasis (accumulation of serum bile acids [sBAs]) with subsequent pruritus, delayed growth and development (failure to thrive), liver injury requiring transplantation, and shortened life expectancy.[2,3]
- Maralixibat (MRX) is a minimally absorbed, selective inhibitor of the ileal apical sodium-dependent bile acid (BA) transporter, interrupting the enterohepatic circulation of BAs, thereby reducing sBAs through fecal BA excretion.[4,5]
- In previously presented work, Week 48 results of a Phase 2, open-label, safety and efficacy study in children with PFIC (INDIGO; NCT02057718) demonstrated growth benefits and improvements in both height and weight, as well as reductions in sBA and pruritus, in children with non-truncating BSEP mutations receiving MRX.[6]

Aim

- To investigate whether changes in the composition of the total sBA pool from baseline (BL) could predict pruritus response in children with non-truncating BSEP mutations treated with MRX during the INDIGO study.

Methods

Study population

- Eligible patients were children (1–18 years of age) with BSEP deficiency (biallelic *ABCB11* or *ATP8B1* mutations) treated with MRX (280 µg/kg/day initially, increased to 560 µg/kg/day at Week 72).
- This analysis focused on those with mild to moderate non-truncating BSEP mutations from BL to 72 weeks.

Analytical methods: Analysis of C_{24} bile acids by tandem mass spectrometry

- Quantitative analysis of the 15 major sBAs was carried out by stable-isotope dilution electrospray ionization liquid chromatography-mass spectrometry (MS)/MS using a fully validated proprietary in-house assay that complies with College of American Pathologists/Clinical Laboratory Improvement Amendments certification. Similarly, 7 alpha-hydroxy-4-cholesten-3-one (sterol-C4) was measured by tandem mass spectrometry.
- Total C_{24} sBA concentrations were calculated from the sum of individual species.

Data analyses

- Primary objective: evaluate changes in sBA subspecies from BL over 72 weeks in children with pruritus response to MRX compared with non-responders.
- Secondary objectives: evaluate the correlation between pruritus (Itch Reported Outcome Observer [ItchRO(Obs)]) and sBA subspecies changes over 72 weeks of MRX treatment in pruritus responders *vs* non-responders, and assess the levels of the BA synthesis marker sterol-C4.
  - ItchRO(Obs) ranges on a 5-point scale (0 = no pruritus and 4 = severe pruritus).
  - Pruritus response was defined as ≥ 1.0 reduction in the ItchRO(Obs) score[7] at ≥ 1 time point.

Statistical methods

- The two-tailed Student's t-test was used to compare groups. Pearson's correlation coefficient was used to analyze ItchRO(Obs) and sBA species changes. Statistical computing was conducted with R.[8]

Results

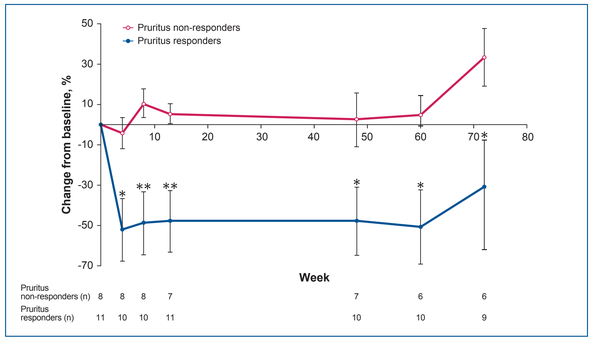
Patient characteristics

- In total, all patients with mild to moderate non-truncating BSEP mutations were included in this analysis (11 responders and 8 non-responders); all were receiving prior and ongoing concomitant ursodeoxycholic acid (UDCA) therapy.
- Patient demographics: mean age was 4.1 years (± standard deviation [SD] 3.4); males n = 13 (68.4%); mean BL levels ± SD: sBA 373.4 ± 162.0 µmol/L, alanine aminotransferase 116.0 ± 109.2 U/L, and total bilirubin 1.8 ± 1.8 mg/dL; mean BL ItchRO(Obs) score was 2.1 ± SD 0.8.

Changes in sBA levels and composition

- Percentage reductions in total sBA levels were significantly greater in responders *vs* non-responders (p < 0.01 to ≤ 0.05; Figure 1).

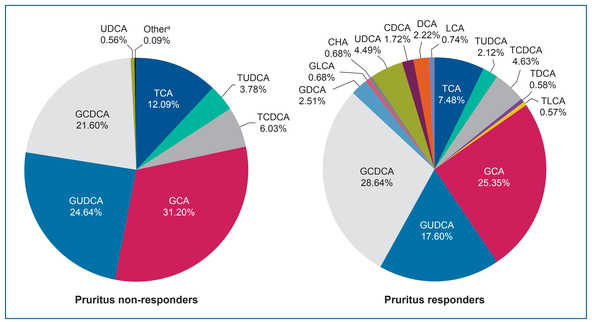
Figure 1. Change in total serum bile acid levels over 72 weeks of maralixibat treatment in pruritus responders *vs* non-responders



*p ≤ 0.05; **p < 0.01 (responders *vs* non-responders); data are mean ± standard error

- A trend toward increased proportions of unconjugated sBAs was observed in responders (9.84 ± standard error [SE] 4.87%) *vs* non-responders (0.61 ± SE 0.24%, p = 0.09; Figure 2).

Figure 2. Composition of serum bile acid following 72 weeks of maralixibat treatment in pruritus responders *vs* non-responders



[a]Includes the following sBAs: CDCA, CHA, DCA, GDCA, GLCA, LCA, TDCA, and TLCA, all ≤ 0.02%
Unconjugated sBAs: CA, CDCA, DCA, LCA, and UDCA; conjugated sBAs: GCA, GCDCA, GDCA, GLCA, GUDCA, TCA, TCDCA, TDCA, TLCA, and TUDCA
CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; GCA, glycocholic acid; GCDCA, glycochenodeoxycholic acid; GDCA, glycodeoxycholic acid; GLCA, glycolithocholic acid; GUDCA, glycoursodeoxycholic acid; LCA, lithocholic acid; sBA, serum bile acid; TCA, taurocholic acid; TCDCA, taurochenodeoxycholic acid; TDCA, taurodeoxycholic acid; TLCA, taurolithocholic acid; TUDCA, tauroursodeoxycholic acid; UDCA, ursodeoxycholic acid

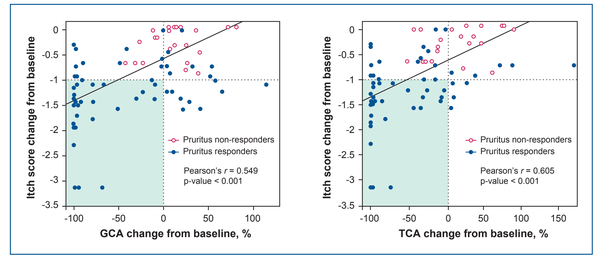
- Greatest reductions were seen in the conjugated sBAs, glycocholic acid (GCA) and taurocholic acid (TCA) (32.1 ± SD 26.2% and 43.3 ± SD 21.2% reductions, respectively; BL *vs* Week 72) in pruritus responders with MRX treatment (Table 1).
- Reductions in GCA and TCA correlated with pruritus reduction in MRX responders (Pearson's *r*: 0.55 and 0.61 for GCA and TCA, respectively; both p < 0.001 *vs* non-responders; Figure 3) despite continued UDCA therapy.

Table 1. Levels of serum bile acid in patients with non-truncating BSEP following 72 weeks of maralixibat treatment compared with baseline

BA hydrophobicity	BA species	Pruritus non-responders			Pruritus responders		
		BL conc., µM (n = 8)	Week 72 conc., µM (n = 6)	p-value[a]	BL conc., µM (n = 11)	Week 72 conc., µM (n = 9)	p-value[a]
Hydrophilic	TCA	36.8	60.5	NS	48.4	29.1	NS
	TUDCA	14.6	22.3	NS	10.2	6.7	NS
	TCDCA	16.2	34.6	NS	18.1	17.3	NS
	GCA	**144.6**	**154.3**	**NS**	**134.5**	**64.1**	**0.06**
	GUDCA	**108.7**	**140.6**	**NS**	**63.8**	**28.2**	**0.09**
	GCDCA	81.9	119.6	NS	71.3	49.2	NS
	CA	0.1	0.1	NS	0.1	0.1	NS
	UDCA	2.1	2.7	NS	2.2	1.2	NS
	CDCA	**0.1**	**0.1**	**NS**	**0.1**	**0.1**	**0.06**
	Total	**405.1**	**534.8**	**NS**	**348.6**	**195.8**	**0.098**
Hydrophobic	TDCA	0.1	0.1	NS	0.6	0.1	NS
	TLCA	0.1	0.1	NS	0.1	0.1	NS
	GDCA	0.1	0.1	NS	1.3	0.2	NS
	GLCA	0.1	0.1	NS	0.1	0.1	NS
	DCA	0.1	0.1	NS	0.1	0.1	NS
	LCA	0.1	0.1	NS	0.1	0.1	NS
	Total	**0.4**	**0.4**	**NS**	**2.2**	**0.7**	**NS**

[a]p < 0.10 was considered to be statistically significant (BL *vs* Week 72); data are mean
BA, bile acid; BL, baseline; BSEP, bile salt export pump; CA, cholic acid; CDCA, chenodeoxycholic acid; conc., concentration; DCA, deoxycholic acid; GCA, glycocholic acid; GCDCA, glycochenodeoxycholic acid; GDCA, glycodeoxycholic acid; GLCA, glycolithocholic acid; GUDCA, glycoursodeoxycholic acid; LCA, lithocholic acid; NS, non-significant; TCA, taurocholic acid; TCDCA, taurochenodeoxycholic acid; TDCA, taurodeoxycholic acid; TLCA, taurolithocholic acid; TUDCA, tauroursodeoxycholic acid; UDCA, ursodeoxycholic acid

Figure 3. Correlation between selected conjugated serum bile acid species change from baseline and reduction in the ItchRO(Obs) score during 72 weeks of maralixibat treatment



p < 0.001 (responders *vs* non-responders); time points include Week 4, 8, 13, 48, 60, and 72; two patients were excluded due to BL ItchRO(Obs) scores of < 1.0
BL, baseline; GCA, glycocholic acid; ItchRO(Obs), Itch Reported Outcome Observer; sBA, serum bile acid; TCA, taurocholic acid

- In pruritus responders, serum sterol-C4 levels increased during treatment, consistent with the biological action of MRX. In non-responders, sterol-C4 levels remained relatively unchanged and were significantly lower *vs* pruritus responders (p < 0.05; Figure 4).

Figure 4. Serum sterol-C4 levels over 72 weeks of maralixibat treatment in pruritus responders *vs* non-responders

*p ≤ 0.05; **p ≤ 0.01 (responders *vs* non-responders); data are mean ± standard error
Sterol-C4, 7 alpha-hydroxy-4-cholesten-3-one

Conclusions

- Pruritus response with MRX treatment in children with non-truncating BSEP deficiency was associated with total and compositional changes in sBA.
- Reductions in GCA and TCA, along with concomitant increases in sterol-C4, were the best predictors of pruritus reduction.
- MRX led to significant reductions in the concentration of the most prevalent hydrophilic sBA subspecies (GCA and GUDCA) from BL to Week 72, consistent with a reduction in BA-driven liver toxicity.
- These findings offer new insight into sBA subspecies changes associated with reductions in cholestasis and pruritus in children with non-truncating BSEP deficiency treated with MRX.

Contact information
Dr. Kenneth Setchell, Kenneth.Setchell@cchmc.org

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Poster presented at The Digital International Liver Congress™ (ILC) 2020, 27–29 August 2020

Acknowledgments
Maralixibat is owned by Mirum Pharmaceuticals Inc. This study was funded by Mirum Pharmaceuticals.
Mirum would like to thank the members of the LUM001-501/INDIGO Study Group.
Editorial assistance was provided by Nina Kureishy, Alpharmaxim Healthcare Communications and funded by Mirum Pharmaceuticals.