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Understanding the Relationship between Systemic and Hepatic Exposure of Obeticholic Acid for the Treatment of Liver Disease in Patients with Cirrhosis

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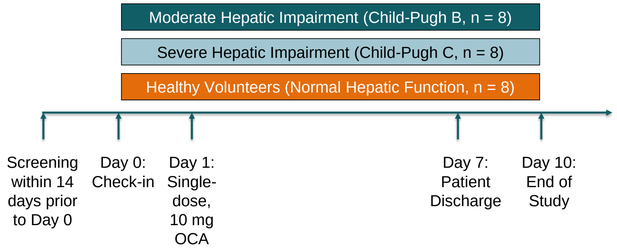
1. INTRODUCTION

- Obeticholic acid (OCA) is a selective and potent farnesoid X receptor (FXR) agonist in development for several chronic liver diseases.
- OCA is a semi-synthetic analogue of chenodeoxycholic acid (CDCA) with similar pharmacokinetic (PK) properties.
- There was a significant increase in systemic exposure of OCA in patients with hepatic impairment. A proportionally similar increase in systemic exposure of endogenous bile acids was also observed in patients with hepatic impairment.
- A physiologic PK model was developed based on a previously reported model for CDCA[1] to define the relationship between systemic and hepatic exposure of OCA (and its pharmacologically active conjugates) in patients with and without hepatic impairment (cirrhosis).

2. METHODS

Figure 1. Study Design in Patients with Hepatic Impairment for Model Recalibration



- 32 volunteers enrolled in the study with no discontinuations or withdrawals.
  - Patients with hepatic impairment: satisfied the criteria of the modified Child-Pugh classification for hepatic impairment during screening
  - Healthy volunteers: absence of clinically-relevant abnormalities identified by a detailed medical history, full physical examination, clinical laboratory tests, and 12-lead ECG

3. RESULTS

Table 1. Demographic Summary for Model Development

Characteristic	Initial Model Calibration	Recalibration for Hepatic Impairment			
		Hepatic Impairment (Child-Pugh Class)			Normal Hepatic Function (n = 8)
	N = 160	Mild (A) (n = 8)	Moderate (B) (n = 8)	Severe (C) (n = 8)	
Female (%)	41	50	25	0	38
White (n)	107	7	6	8	8
Not Hispanic or Latino (n)	69	7	6	3	4
Day 0 Child-Pugh Score	NA	5.9 (0.4)	7.8 (0.9)	10.4 (0.5)	NA
Hepatic Impairment (n)					
Hepatitis C only	NA	1	1	0	NA
Cirrhosis only	NA	1	2	3	NA
Hepatitis C + cirrhosis	NA	5	5	5	NA
Other	NA	1	0	0	NA
Age (y)	37.0 (9.8)	57.1 (5.2)	55.1 (5.1)	53.5 (6.1)	54.3 (6.5)
Height (cm)	170 (9.6)	167 (9.2)	171 (10.5)	166 (9.2)	169 (9.2)
Weight (kg)	76.4 (11.8)	77.7 (13.9)	88.9 (15.7)	78.1 (22.6)	82.2 (14.9)

Data are mean (SD) where applicable

3. RESULTS

Figure 2. Total OCA Concentrations Increase with Worsening Hepatic Impairment

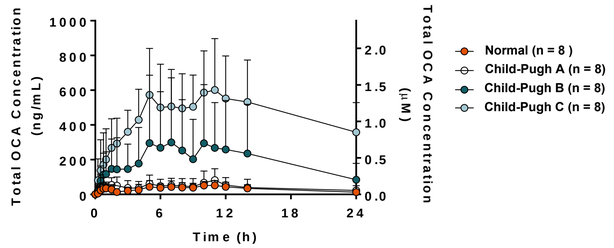
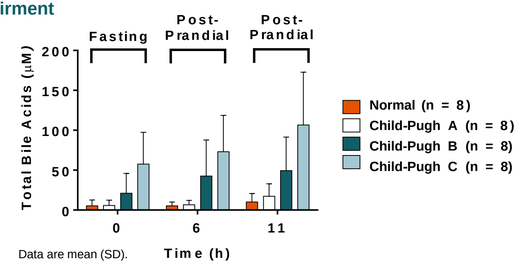


Table 2. Pharmacokinetic Parameters

	Normal Hepatic Function (n = 8)	Hepatic Impairment (Child-Pugh Class)		
		Child-Pugh A (n = 8)	Child-Pugh B (n = 8)	Child-Pugh C (n = 8)
C_{max} (µM)	0.16 (0.07)	0.25 (0.15)	0.83 (0.90)	1.60 (0.67)
AUC_t (µM·hr)	5.89 (4.29)	6.58 (4.90)	37.30 (45.31)	97.56 (51.99)
AUC_{24} (µM·hr)	1.78 (1.01)	2.42 (2.27)	11.20 (12.78)	25.90 (10.89)

Data are mean (SD), Total OCA concentrations includes OCA and its conjugates. Bile acid concentrations were determined by LC-MS/MS.

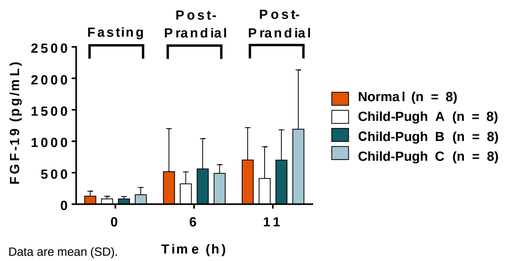
Figure 3. Plasma Endogenous Bile Acids Increase with Worsening Hepatic Impairment



Data are mean (SD).

- Endogenous bile acids also increase in the plasma to an extent similar to Total OCA with hepatic impairment. This is consistent with the hypothesis that OCA behaves pharmacokinetically like endogenous bile acids.

Figure 4. Plasma FGF-19 Concentration Consistent Regardless of Hepatic Impairment



Data are mean (SD).

- FGF-19 levels were higher for all groups at 6 and 11 hours post-dose relative to pre-dose suggesting that OCA is capable of activating FXR regardless of hepatic impairment.
- No obvious trends in FGF-19 levels versus hepatic impairment were observed.

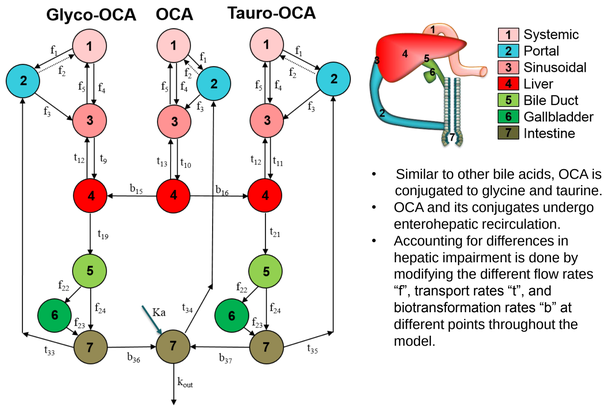
Model Development

- The initial basis of the model was derived from the model by Molino et al to describe the physiologic PK of CDCA.[1]
- The model for OCA was calibrated by the plasma concentration and time profiles of OCA, glyco-OCA and tauro-OCA in healthy volunteers with normal hepatic function from a single dose of 10 mg OCA, then recalibrated for patients with hepatic impairment taking a single 10 mg dose of OCA.

Table 3. Recalibration Parameters

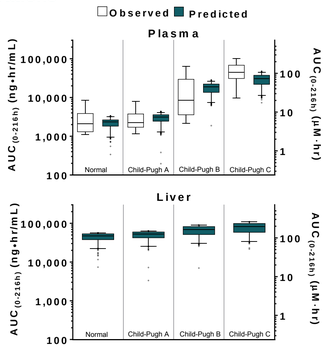
Mechanism	Normal	Mild	Moderate	Severe
1. Decreased hepatic uptake (mean of OCA, glyco-OCA, and tauro-OCA)[2,3]	77%	74%	34%	24%
2. Portal systemic shunting (% Shunted)[3,4]	0%	9%	37%	45%
3. Decreased functional liver volume (% of normal volume)[5]	100%	89%	71%	61%
4. Increased taurine conjugation (Glycine/Taurine ratio)[6]	4.6	4.6	1.6	1.0

Figure 5. Physiologic PK Model Diagram



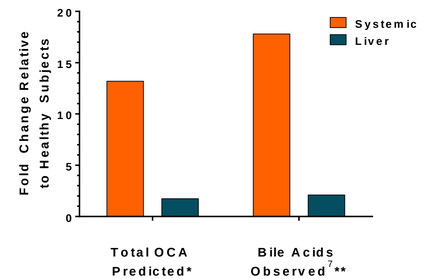
- Similar to other bile acids, OCA is conjugated to glycine and taurine.
- OCA and its conjugates undergo enterohepatic recirculation.
- Accounting for differences in hepatic impairment is done by modifying the different flow rates "f", transport rates "t", and biotransformation rates "b" at different points throughout the model.

Figure 6. Plasma OCA Concentrations are a Poor Surrogate for Liver OCA Concentrations



n = 8 for observed values. Predicted values were estimated using a 200 replicate simulation from the physiologic PK model of OCA (n = 1600). Boxplot whiskers represent 1st to 99th percentile.

Figure 7. Systemic vs Liver Bile Acids Consistent with the Literature



*Total OCA predicted using a physiologic PK model assuming Child-Pugh Score C.
**Serum and Hepatic Bile Acid Concentration in End-Stage Liver Disease.

- Liver exposure of total OCA is predicted to be ~2-fold greater in patients with severe hepatic impairment (Child-Pugh C) relative to healthy patients.
- Liver exposure of bile acids has been reported to be ~2-fold greater in patients with end-stage liver disease relative to healthy patients.

4. CONCLUSIONS

- The physiologic PK model for OCA-predicted plasma exposures showed good agreement with observed exposures in healthy volunteers and patients with hepatic impairment.
- Systemic exposure of OCA was predicted to be 1.4-, 8.0-, and 13-fold greater in patients with mild, moderate, and severe hepatic impairment, based on Child-Pugh score, than in healthy patients which is consistent with observed results.
- Liver exposure of OCA was predicted to be 1.1-, 1.5- and 1.7-fold greater in patients with mild, moderate, and severe hepatic impairment than that of healthy patients.
- These results highlight that although significantly higher systemic exposure of OCA is expected with hepatic impairment only a modest increase in liver exposure is expected.
- Modeling results and clinical trial data support the safety and efficacy of OCA in patients with primary biliary cirrhosis (PBC) who have cirrhosis to be treated with therapeutic doses used in non-cirrhotic patients.

5. REFERENCES

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6. DISCLAIMER

Obeticholic acid (OCA) is an investigational drug. It is not approved for use by the FDA, EMA or any other regulatory body. No conclusions can be drawn concerning the safety or efficacy of OCA at this time.

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