Inhibition of bile acids synthesis *via* fibroblast growth factor 19 (FGF19) through intestinal signaling: A population analysis

Dina Chernikova[1], Victor Sokolov[1], Veronika Voronova[1], Amani Al-Khaifi[3,5], Sara Straniero[3,5], Mats Rudling[3,5], Chanchal Kumar[4,5], Kirill Peskov[1], Gabriel Helmlinger[2], Bo Angelin[3,5]

[1]M&S Decisions, Moscow, Russia, [2]AstraZeneca, Waltham, USA, [3]Metabolism Unit, Karolinska Institutet at Karolinska University Hospital Huddinge, Stockholm, Sweden, [4]Cardiovascular and Metabolic Diseases Innovative Medicines, AstraZeneca R&D, Mölndal, Sweden, [5]Karolinska Institutet/AstraZeneca Integrated CardioMetabolic Center (KI/AZ ICMC), Department of Medicine, Novum, Huddinge, Sweden.

Executive summary

Regulation of bile acid (BA) synthesis is mediated through the farnesoid X receptor (FXR), which is predominantly expressed in the liver and intestine [1]. The role of direct interaction of BAs with hepatic FXR versus the influence of FGF19 which is secreted from the small intestine after BA-mediated FXR activation is still unclear [2, 3].

The objective of this analysis was to evaluate the role of intestinal signaling *via* FGF19 in the inhibition of BA synthesis and identify a possible time lag between FGF19 and individual BAs.

Introduction

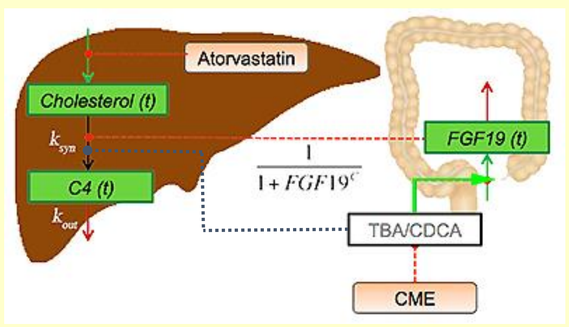
- FXR-mediated FGF19 synthesis is up-regulated by BA reabsorption from the intestine.
- BA production in the liver can be regulated by FGF19 through FGF-receptor-4/beta-Klotho signaling and by BA-activated intracellular FXR.
- *De novo* BA synthesis is monitored by 7-alpha-hydroxy-4-cholesteryl-3-one (C4), a marker of cholesterol 7-alpha-hydroxylase (CYP7A1) activity.

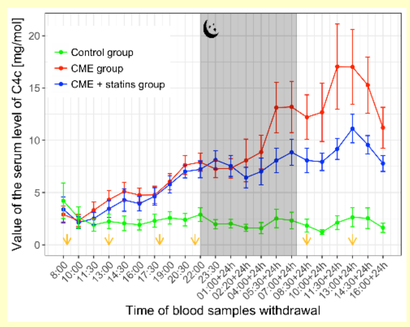
Methods

DATA for analysis were obtained from 11 healthy volunteers under sequential treatment with cholestyramine (CME) (4g QID), CME preceded by atorvastatin (40 mg daily), and w/o treatment.

THE MODEL describing the functional relationship between FGF19 and C4 was obtained based on an analytical solution of the corresponding system of differential equations.

Figure 1. The model scheme and C4 time-profiles in 3 groups





The model describes time-dependent behavior of C4 in Control (no treatment), CME, and CME preceded by atorvastatin groups. Time-dependent FGF19 and cholesterol plasma levels were used directly from the experimental data.

The following functional form was used to describe the time-dependent behavior of C4:

$$C4(t) = (1 - e^{-tk_{out}})Cholesterol(t)\frac{k_{syn}}{1+FGF19(t)^C} + Cholesterol(t)\frac{C4(t=0)}{Cholesterol(t=0)}e^{-tk_{out}}$$

STATISTICAL ANALYSIS was performed using a sample cross-covariance function between two time series, y_{1t} and y_{2t} ($c_{y1,y2}(k)$), at lags k = 0, ±1, ±2,... in R and MATLAB, to investigate time correlations of FGF19/C4, FGF19/BA and BA/C4:

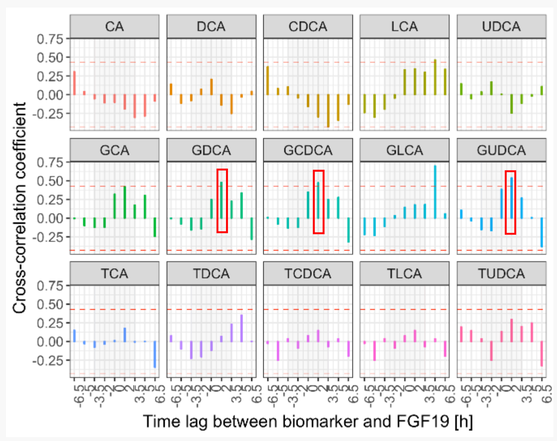
$$c_{y_1y_2}(k) = \begin{cases} \frac{1}{T}\sum_{t=1}^{T-k}(y_{1t} - \bar{y}_1)(y_{2,t+k} - \bar{y}_2);\ k = 0, 1, 2, \ldots \\ \frac{1}{T}\sum_{t=1}^{T+k}(y_{2t} - \bar{y}_2)(y_{1,t-k} - \bar{y}_1);\ k = 0, -1, -2, \ldots \end{cases},$$

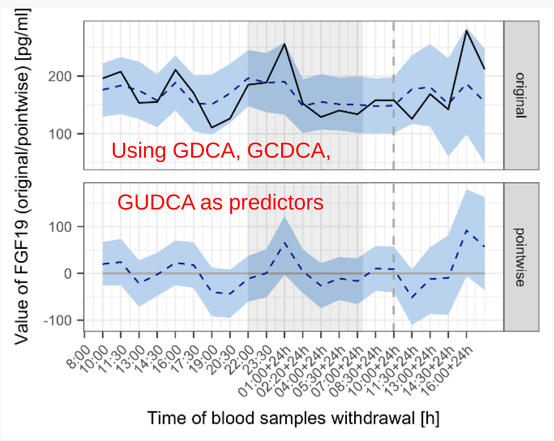
Bayesian structural time-series model and the Granger causality test are used to determine which time series may forecast another.

Results

The sample cross-correlation analysis revealed the presence of strong positive correlations with a **time lag of 2 hours (0h - 3.5 h)** between glycine-conjugated bile acids (GDCA, GCDCA, GUDCA) and FGF19.

Figure 2. Cross-correlation of BA and FGF19 (Control group) and a Bayesian structural time-series model for FGF19 and GDCA, GCDCA, GUDCA as predictors



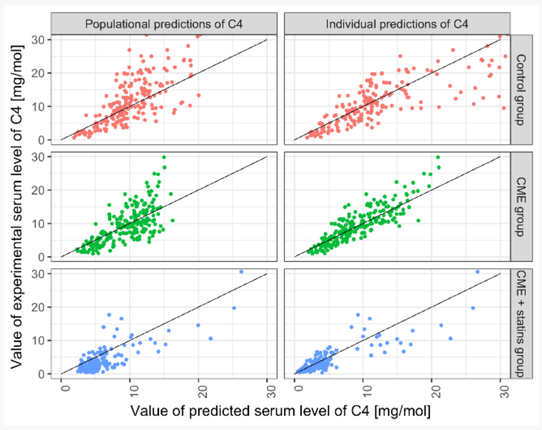


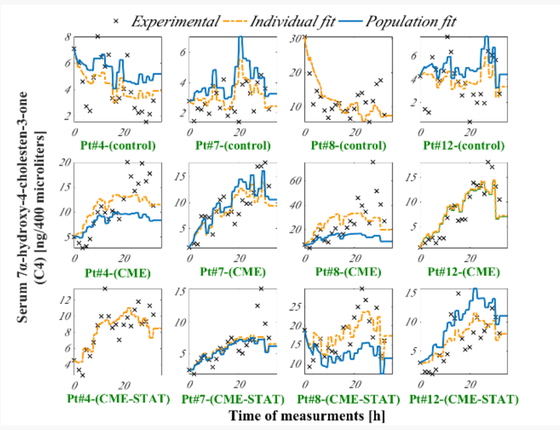
BA	$r_{y1,y2}(2)$	p-value
GDCA	0.477	0.025
GCDCA	0.473	0.026
GUDCA	0.537	0.012

According to the Granger causality test, the sum of responses of GDCA, GCDCA, GUDCA "Granger-causes" the response of FGF19 with a lag of 2 h (p-value =0.04825).

The analytically-obtained functional relationship between FGF19 and C4 reproduced the central trend and, partially, the variability in the observed data. Values of the population parameter estimates revealed an inverse square root dependence of CYP7A1 activity on negative feedback mechanism.

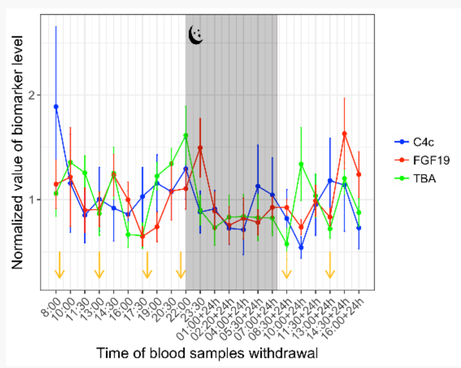
Figure 4. Measurements vs. predictions (l.h.s) and individual/population fits (r.h.s.)





Both nonlinear mixed-effects analysis and the Bayesian structural time-series model indicate that the role of FGF19 in the inhibition of BA synthesis may be overestimated in comparison with other regulating mechanisms.

Figure 5. The dynamics of C4, FGF19 and Total BA in control group (time-profiles)



No statistically significant cross-correlations were observed between FGF19 and C4 solely, and Total BA and C4.

Conclusions

- Strong positive correlations with a time lag of 2 hours between GDCA, GCDCA, GUDCA and FGF19
- The empirical functional relationship between FGF19 and C4 well reproduced the central trend and, partially, the variability in the observed data in the CME, control and CME/atorvastatin groups

References

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Contact info: dina.chernikova@msdecisions.ru

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Karolinska Institutet