A SEMI-MECHANISTIC MODEL OF FIBROSIS PROGRESSION USING COLLAGEN PROPORTIONATE AREA (CPA) IN POST LIVER TRANSPLANT (POLT) PATIENTS WITH CHRONIC HEPATITIS C (CHC)

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BACKGROUND

Quantitative measurements of collagen proportionate area (CPA) by digital image analysis quantifies fibrosis in the liver. A semi-mechanistic model was developed to describe CPA progression in POLT CHC patients.

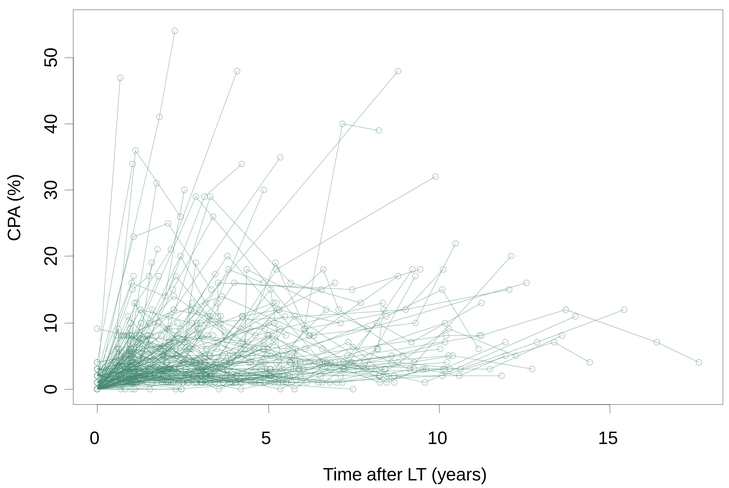
AIM

To build a semi-mechanistic model of progression of CPA for POLT CHC patients and explore potential patient characteristics affecting quantity of liver fibrosis.

METHODS

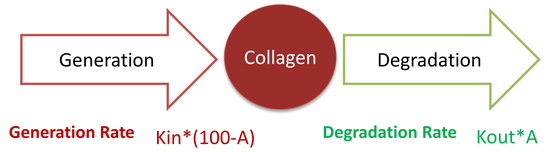
Longitudinal CPA data together with demography, HCV genotype, medical and immunosuppressive therapy from 185 consecutive POLT CHC patients [Figure. 1] were included in the model. Assumptions regarding generation and degradation mechanisms for collagen [Figure. 2] were made for CPA modeling. Fixed effects and inter-subject variability (ISV) were estimated by a nonlinear mixed effects modeling technique. Acute HCV, basic immunosuppression, and donor age were potentially associated with CPA progression. The covariates in the model were selected by a stepwise forward inclusion (p< 0.05) and backward (p< 0.005) exclusion method.
The model was evaluated using graphical and numerical diagnostic tools [Figure. 3].

Figure. 1 CPA Raw Data from 185 consecutive POLT CHC patients



Pharmacometrics, Global Clinical Pharmacology

Figure. 2 Base Model Structure Interpretation



$$\frac{dA}{dt} = k_{in} \cdot (100 - A) - k_{out} \cdot A$$

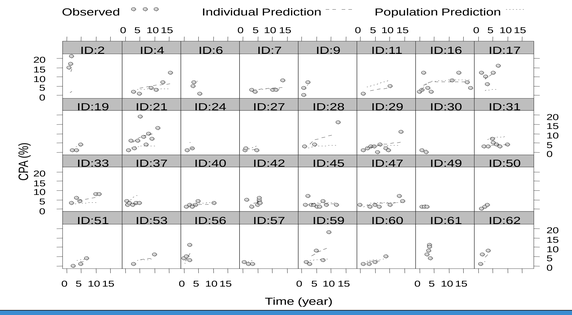
100-A: Normal Liver Proportion

A : Collagen Proportion

Tested Structures:

			OFV	
	1	$\frac{dA}{dt} = k_{in}$	2848.56	Collagen generation is at a constant rate. No collagen degradation component.
	2	$\frac{dA}{dt} = k_{in} \cdot A$	4384.96	Collagen generation is associated with collagen proportion. No collagen degradation component.
☑	3	$\frac{dA}{dt} = k_{in} \cdot (100 - A) - k_{out} \cdot A$	2841.11	Collagen generation is associated with normal liver proportion, while collagen degradation is associated with collagen proportion.

Figure. 3 Examples of Individual Predictions /Goodness of Fit Plot



RESULTS

The analysis showed that acute HCV, basic immunosuppression, and number of immunosuppressive regimens impacted collagen generation rate while donor age was correlated with collagen degradation rate. After covariate forward inclusion and backward exclusion steps, the following model best fitted patients' CPA progression data:

$$\frac{dCPA}{dt} = (k_{in} + AHC + BI) \cdot (100 - CPA) - k_{out} \cdot CPA$$

where Kin is generation rate, Kout is degradation rate, AHC = acute HCV status, and is a binary variable (0=NO; 1=YES), BI = basic immunosuppression, and is binary (0=cyclosporine, 1=tacrolimus).
Estimated Kin and Kout were 0.019 and 0.48, respectively. ISV was 67% and 92% for Kin and Kout, respectively. Patients with tacrolimus treatment appeared to have their collagen generation rate increased by 0.027 compared to those with cyclosporine treatment. Patients with acute HCV appeared to have their collagen generation rate increased by 0.016 compared to those without acute HCV.

Figure. 4 Observed and Predicted CPA Stratified by Basic Immunosuppression and Acute HCV status

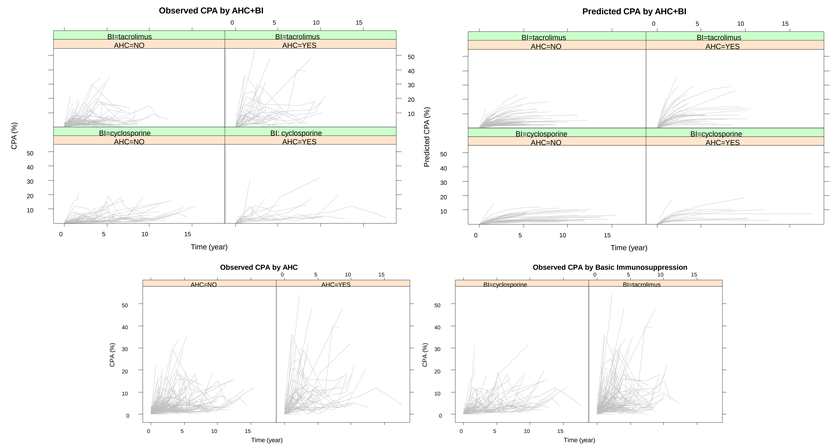
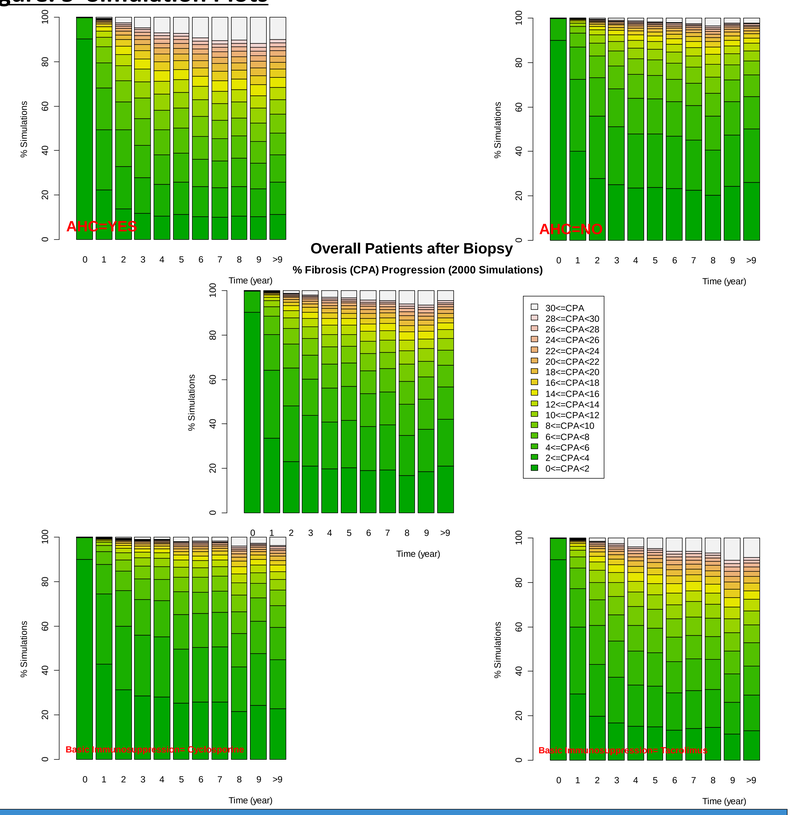


Figure. 5 Simulation Plots



CONCLUSIONS

A mechanism-based methodology could be applied to model CPA progression. A semi-mechanistic CPA progression model developed from POLT CHC patients suggests that use of tacrolimus and acute HCV infection significantly increase the rate of collagen generation [Figure. 4 and Figure. 5]. The CPA model may evolve with further investigation of mechanisms of collagen generation and degradation and exploration of variations of immunosuppression.